Organic Chemistry Part 2

CHAPTER 5

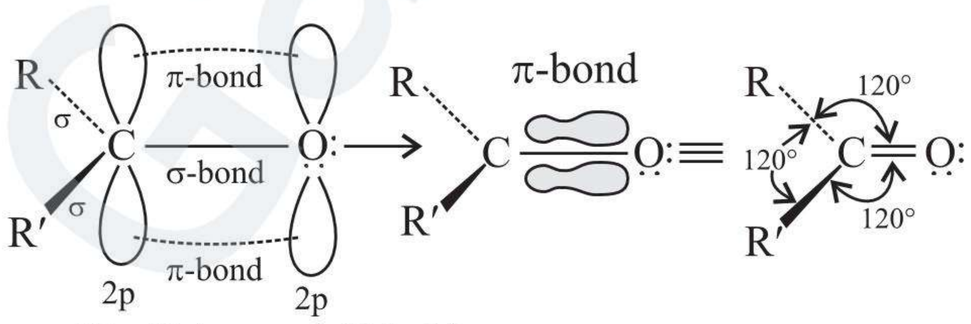
5 Aliphatic and Aromatic Aldehydes and Ketones

5.1 INTRODUCTION

A carbonyl group is a functional group that comprises carbon atom double-bonded to an oxygen atom (C═O). Compounds that have the carbonyl group are called carbonyl compounds. In aldehydes, the carbonyl group is attached to a C and H while in ketones, it is bonded to two C atoms. The general formulae of these compounds are given below:

5.2 STRUCTURE OF THE CARBONYL GROUP

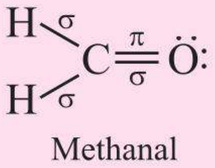
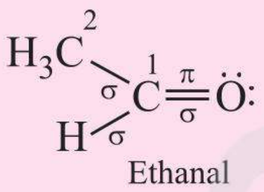
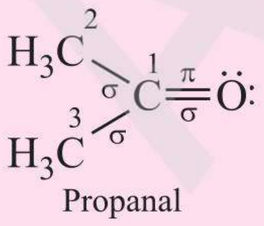
The C atom of (C═O) group is sp^2-hybridised and forms three σ-bonds and one π-bond formed by the overlap of pure $2p$-orbital of C atom with $2p$-orbital of O atom. The O atom has two LP $\bar{e}$'s; thus the C atom of (C═O) group and three atoms attached to it are on the same plane with bond angle of 120° and the π $\bar{e}$ cloud is above and below the plane.



(R′ = H, in case of aldehyde)

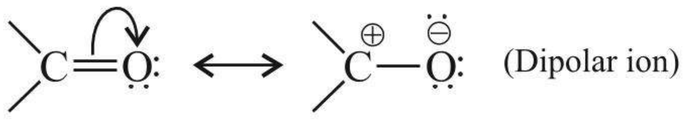
Fig. 5.1 Orbital diagram for the formation of carbonyl group

Table 5.1 Bond formation in aldehyde and ketones

S.No.	Compound	Bond formation	
1.	 Methanal	2 σ-bonds (C—H) ⇒	Formed by the overlap of sp^2 (C) with $1s$ (H).
		1 σ-bond (C—O) ⇒	Formed by the overlap of sp^2 (C) with sp^2 (O).
		1 π-bond (C—O) ⇒	Formed by the overlap of pure $2p$ (C) with pure $2p$ (O).
		2 LP $\bar{e}$'s ⇒	Present in two sp^2 orbitals of O atom.
2.	 Ethanal	1 σ-bond (C_1—C_2)⇒	Formed by the overlap of sp^2 (C_1) with sp^3 (C_2).
		1 σ-bond (C_1—H) ⇒	Formed by the overlap of sp^2 (C_1) with $1s$ (H).
		1 σ-bond (C_1—O) ⇒	Formed by the overlap of sp^2 (C_1) with sp^2 (O).
		1 π-bond (C_1—O) ⇒	Formed by the overlap of pure $2p$ (C_1) with pure $2p$ (O).
		3 σ-bonds in CH_3 (C_2—H) ⇒	Formed by the overlap of sp^3 (C_2) with $1s$ (H).
		2 LP $\bar{e}$'s ⇒	Present in two sp^2 orbitals of O atom.
3.	 Propanal	2 σ-bonds (C_1 — C_2) and (C_1—C_3) ⇒	Formed by the overlap of sp^2 (C_1) with sp^3 (C_2) and sp^3 (C_3).
		1 σ-bond (C_1—O) ⇒	Formed by the overlap of sp^2 (C_1) with sp^2 (O).
		1 π-bond (C_1—O) ⇒	Formed by the overlap of pure $2p$ (C_1) with pure $2p$ (O).
		2 LP $\bar{e}$'s ⇒	Present in two sp^2 orbital of O atom.
		6 σ-bonds in 2 (CH_3) groups (C_2—H) and (C_3—H) ⇒	Formed by the overlap of sp^3 (C_2) and sp^3 (C_3) with $1s$ (H).

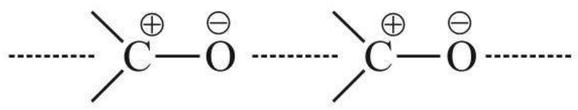
5.2.1 Polarity and Boiling Point of Carbonyl Compounds

The (C═O) bond is polarised due to high EN of O atom relative to C atom, as shown below.



Thus the C atom acts as electrophile (Lewis acid) and O atom as nucleophile (Lewis base). Therefore, carbonyl compounds have some dipole moment and are more polar than ether.

There is an interaction among bond dipoles. These interactions are called as dipole–dipole interaction and due to these interactions molecules are held quite strongly.

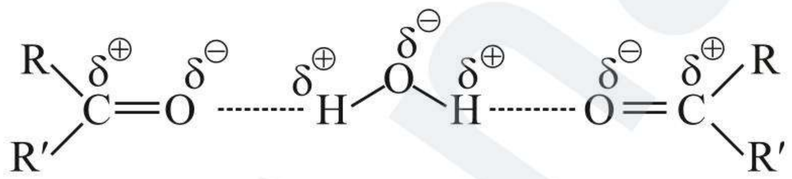


a. Boiling points: Boiling points of carbonyl compounds are higher than hydrocarbons and ethers of comparable molecular masses but lower than those of **alcohols and carboxylic acids** of comparable molecular masses due to the absence of intermolecular H-bonding (alcohols and acids both form H-bonding, but acids form dimer).

Table 5.2 Boiling points of different compounds of comparable molecular masses

S.No.	Compound and molecular mass	B.P. (K)
1.	*n*-Butane (58)	273
2.	Me—O—Et (Methoxy ethane) (60)	281
3.	$MeCH_2CHO$ (Propanal) (58)	322
4.	MeCOMe (Acetone) (58)	329
5.	$MeCH_2CH_2OH$ (Propan-1-ol) (60)	370

b. Water solubilities: Lower members of carbonyl compounds such as methanal, ethanal, and propanone (acetone) are miscible with H_2O because they form H-bonding with water.



But the solubility of carbonyl compounds decreases with the increase in C-chain because non-polar part increases. However, branched carbonyl compounds are more soluble in H_2O than the straight-chain carbonyl compounds, since on branching the surface area decreases and solubility increases.

Unlike solubility, boiling points of straight-chain carbonyl compounds are higher than those of branched carbonyl compounds, since more is the surface area, higher is the boiling point.

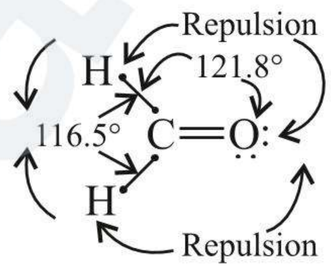
All carbonyl compounds are fairly soluble in organic solvents such as benzene, ether, methanol, chloroform, etc.

Methanal is a gas at room temperature, ethanal is a volatile liquid, and other carbonyl compounds are liquid or solid at room temperature.

The lower aldehydes have sharp pungent odours. As the size of the molecule increases, the odour becomes less pungent and more fragrant. Due to this, various naturally occurring carbonyl compounds are used in the prepara-tion of perfumes and as flavouring agents.

5.2.2 (H—C—O) and (H—C—H) Bond Angles in Methanal (CH_2═O)

Due to repulsion by the electronegative O atoms on the $\bar{e}$'s in the (C—H) bonds, the (H—C—O) bond angle is slightly greater than the expected 120° (121.8°) and thus (H—C—H) bond angles are slightly less than 120° (116.5°).



5.2.3 Comparison of Polarities of (C═O) and (C═C) Bonds

The (C═C) group has no significant polar character, but (C═O) group has polar character since O atom is more electronegative than C atom. Further, (C═C) group is polarised with $C^{\delta+}$ and $O^{\delta-}$, in which $\overset{\delta-}{O}$ acts as nucleophilic site and $C^{\delta+}$ acts as electrophilic site. On the contrarory, the π-bond of (C═C) bond is an $\bar{e}$ source and acts as nucleophilic site.

Illustration 5.1

Give the decreasing order of boiling points of the following:

a. (I) Butanal (II) Butan-1-ol
(III) Diethyl ether (IV) Pentane

b. (I) Propan-2-ol (II) Propan-2-one
(III) 2-Methyl propene

Sol.

a. All compounds are of comparable molecular masses (72 to 74). (II) is alcohol and forms intermolecular H-bonding, and thus boiling point of (II) would be highest. (I) is aldehyde and has dipole–dipole interaction, and thus boiling point of (I) would be higher than that of ether (III). (IV) is alkane, having only weak van der Waals forces.

Hence, the decreasing order of boiling points is as follows:
(II) > (I) > (III) > (IV)

b. All compounds are of comparable molecular masses: (I) is alcohol, (II) is ketone, and (III) is alkene.

Boiling points of alcohol > ketone > alkene [as explained in part (a) above].

The decreasing order of boiling points is as follows:

(I) > (II) > (III)

ILLUSTRATION 5.2

Explain:

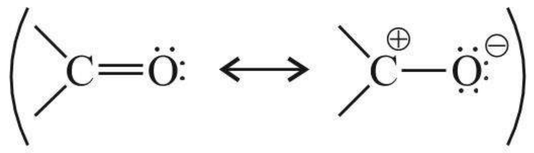
a. Dipole moment of $MeCH_2CHO$ (propanal) (2.5 D) is greater than that of but-1-ene (0.3D).

b. Enthalpy of combustion ($\Delta H°_c$) of butanal is greater than that of butan-2-one.

c. Enthalpy of hydrogenation ($\Delta H°_h$) of pent-3-en-2-one (I) is lower than that of pent-4-en-2-one (II).

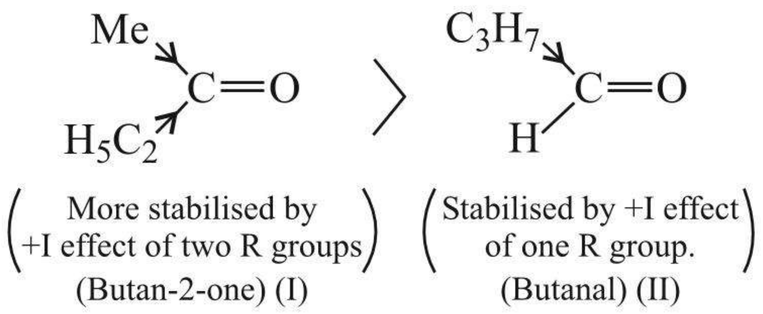
Sol.

a. Dipole moment of carbonyl compounds is greater than that of alkenes due to more polar resonance structure.



b. More $\bar{e}$-donating group (EDG) stabilises the (C═O) group by releasing $\bar{e}$'s to the sp^2-hybridised C atom. More stable the carbonyl compound, lower is $\Delta H°_c$ of combustion.

Ketones have two alkyl groups, while the aldehyde has only one.



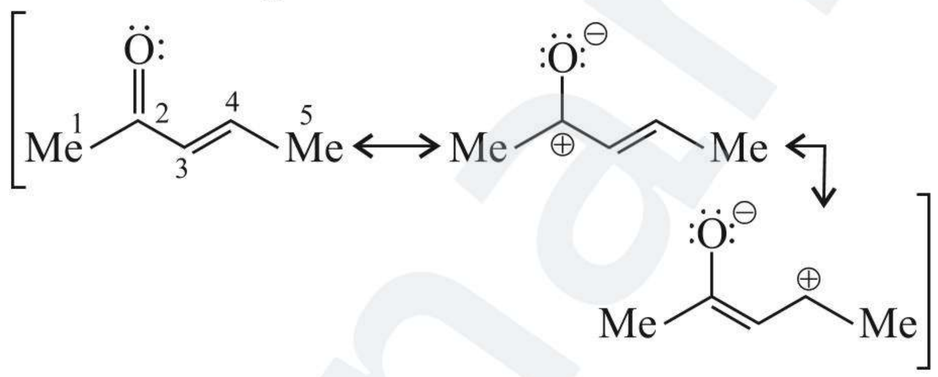
(Butan-2-one) (I) — More stabilised by +I effect of two R groups

(Butanal) (II) — Stabilised by +I effect of one R group.

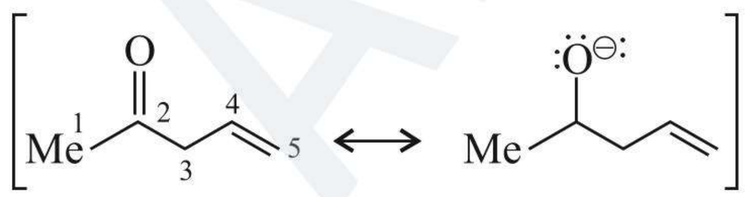
$\Delta H°_c$ of I < $\Delta H°_c$ of (II).

c. More stable is the carbonyl group, lesser is the enthalpy of hydrogenation.

(I) is resonance stabilised due to conjugation and thermodynamically more stable than (II) and as a result has lower $\Delta H°_h$.



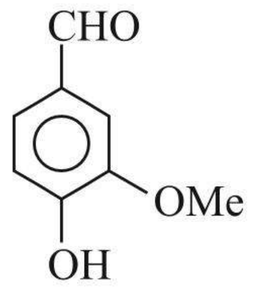
[(I) is more resonance stabilised because (C═O) and (C═C) are in conjugation]



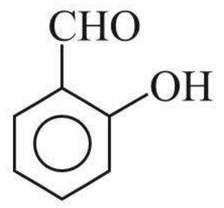
[Less resonance stabilisation of (II), since (C═O) and (C═C) are not in conjugation.]

5.2.4 Uses of Aldehydes and Ketones

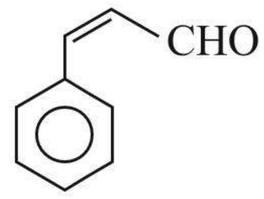
Aldehydes and ketones are found in plants and animals. They play an important role in the biochemical process of life. They are used as flavouring agents; for example, vanillin (from vanilla beans), salicylaldehyde (from meadow sweet), and cinnamaldehyde (from cinnamon) have pleasant fragrance.



Vanillin



Salicylaldehyde



Cinnamaldehyde

They are used in many food products and pharmaceuticals to add flavours. They are also used as solvents (e.g., acetone) and for preparing adhesives, paints, resins, perfumes, plastics, fabrics, etc.

The 40% aqueous solution of formaldehyde, known as formalin, is used to preserve biological species and to prepare bakelite (a phenol–formalindehyde resin), urea–formaldehyde glues, and other polymeric products. Acetaldehyde is used in the manufacture of acetic acid, ethyl acetate, vinyl acetate, polymers, and drugs. Benzaldehyde is used in perfume and dye industries.

Butyraldehyde, vanillin, acetophenone, and camphor are used as flavouring compounds.

5.2.5 TEST OF CARBONYL COMPOUNDS

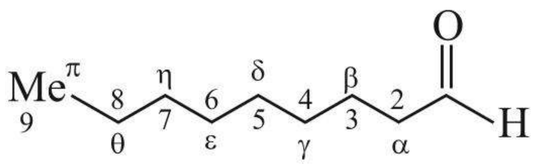
Both aldehydes and ketones give coloured precipitates with 2,4-DNP (Brady's reagent). Positive DNP test shows the presence of (C═O) group. Aldehydes are distinguished from ketones with Tollens or Fehling's or Benedict's or Schiff's reagent (see Chapter 2).

5.3 NOMENCLATURE

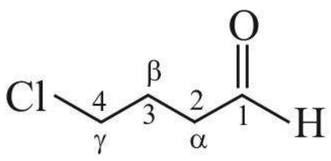
a. Common names of aldehydes: The common names of most aldehydes are derived from the common names of corresponding carboxylic acids by replacing the ending *-ic* of acid with aldehyde. The location of substituents in the C-chain is indicated by Greek letters, α, β, γ, δ, ε, η, θ, etc. The α-C is the one directly linked to the aldehyde group, β-C is next, and so on.

For example:

i.



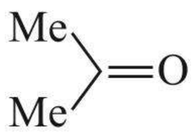
ii.

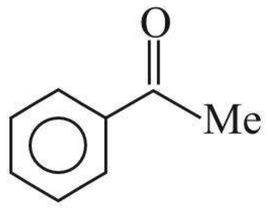


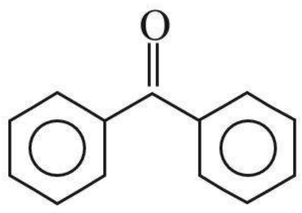
γ-Chlorobutyraldehyde

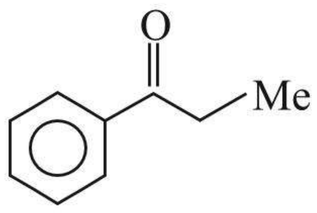
b. Common names of ketones: Their common names are derived by naming two alkyl or aryl groups bonded to (C═O) group. The locations of substituents are indicated by Greek letters, α, α', β, β', and so on, beginning with C atoms next to (C═O) group, indicated as α, α'. Dimethyl ketone has historical name and is called acetone. Alkyl phenyl ketones are named by adding the acyl group as prefix to phenone.

For example,


Acetone


Acetophenone

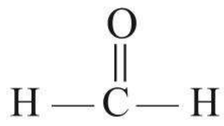

Benzophenone

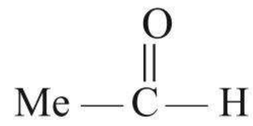

Propiophenone

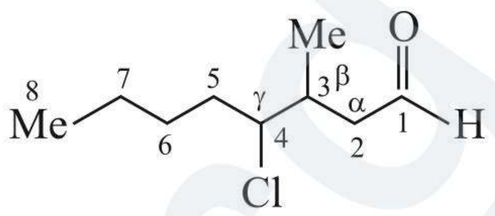
c. IUPAC names: The IUPAC names of aliphatic aldehydes and ketones are derived from the names of the corresponding alkanes by replacing the ending -e with -al and -one, respectively. Longest chain rule, starting from (CHO) group is followed in aldehydes.

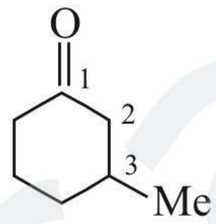
In ketones, the numbering begins from the end nearer to the (C═O) group. The substituents are prefixed in alphabetical order along with numerals indicating the position in C-chain. In cyclic ketone, (C═O) group is numbered one. In cyclic aldehydes, the suffix carbaldehyde is added after the full name of cycloalkane. The numbering of the ring C atoms starts from the C atom attached to the (—CHO) group.

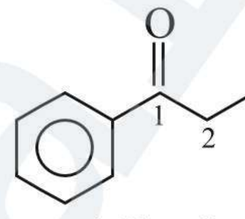
IUPAC name of benzaldehyde (common name) is benzene carbaldehyde. For example:

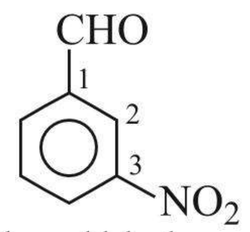

(IUPAC): (Methanal)
(Common): (Formaldehyde)

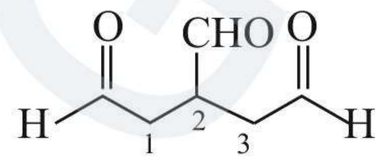

(Ethanal)
(Acetaldehyde)


(4-Chloro-3-methyl octan-1-al)
(γ-Chloro-β-methyl octyraldehyde)


3-Methylcyclo hexanone


1-Phenyl-butan-1-one


3-Nitrobenzaldehyde or 3-Nitrobenzene carbaldehyde


Propane-1,2,3-tricarbaldehyde

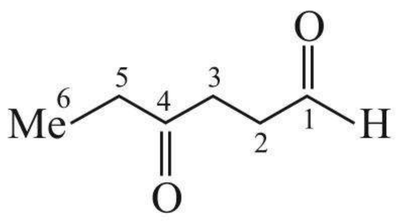
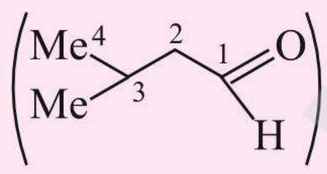
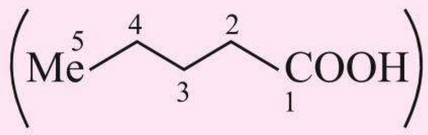
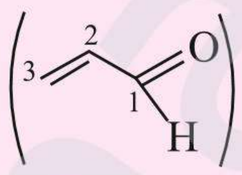
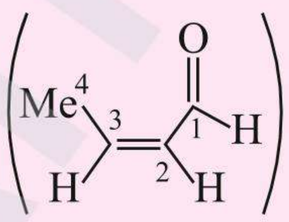
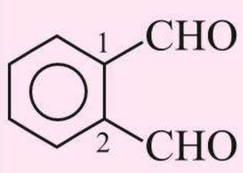
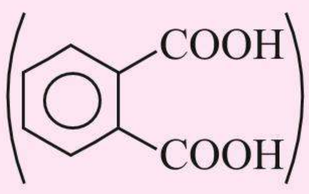
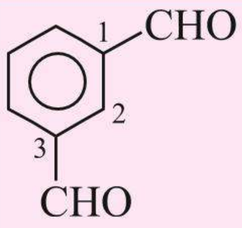
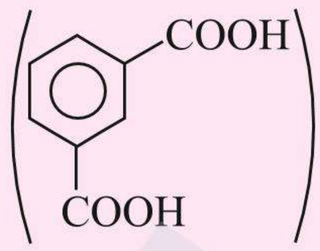
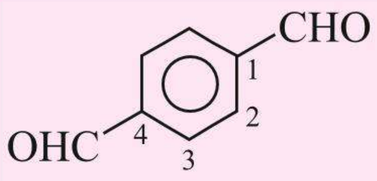
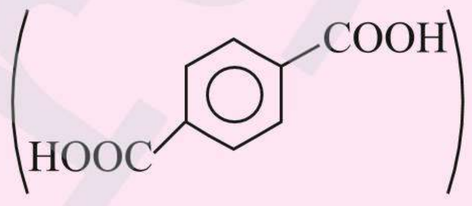
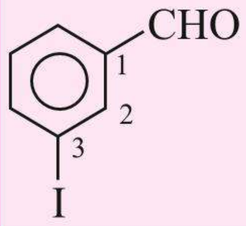
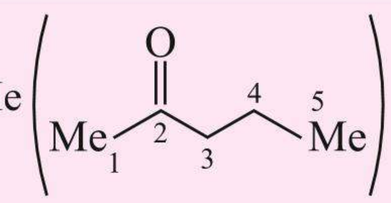
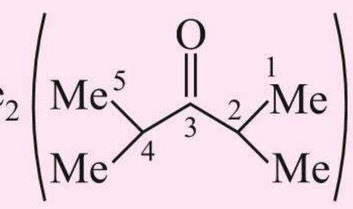
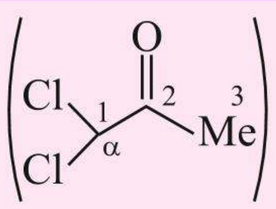
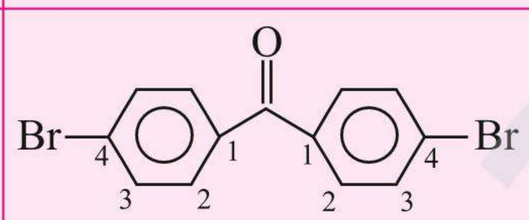

4-Oxohexan-1-al

Table 5.3 IUPAC and common names of aldehydes and ketones

S.No.	Structure	IUPAC name	Common names
ALDEHYDES			
1.	HCHO	Methanal	Formaldehyde
2.	Me — CHO	Ethanal	Acetaldehyde
3.	Me_2CHCH_2CHO 	3-Methyl butan-1-al	Isovaleraldehyde (Derived from valeric acid) 
4.	$CH_2{=}CH-CHO$ 	Propen-1-al	Acrolein or acryaldehyde
5.	$CH_3-C(H){=}C(H)-CHO$ 	(Z)- or *cis*-But-2-en-1-al	*cis*-Crotonaldehyde
6.		Benzene-1,2-dicarbaldehyde	Phthaldehyde (Derived from phthalic acid) 

7.		Benzene-1,3-dicarbaldehyde	Isophthaldehyde (Derived from isophthalic acid) 
8.		Benzene-1,4-dicarbaldehyde	Terephthaldehyde (Derived from terephthalic acid) 
9.		3-Iodobenzaldehyde	*m*-Iodobenzaldehyde
KETONES			
10.	$MeCOCH_2CH_2Me$ 	Pentan-2-one	Methyl-*n*-propyl ketone
11.	$Me_2CHCOCHMe_2$ 	2,4-Dimethyl pentan-3-one	Diisopropyl ketone
12.	$Cl_2CHCOMe$ 	1,1-Dichloro propan-2-one	α,α-Dichloroacetone
13.		Bis-(4-bromophenyl) methanone	Di-(*p*-bromophenyl) ketone

5.4 PREPARATION OF ALDEHYDES AND KETONES

5.4.1 By Oxidation of Alcohols

1° and 2° alcohols on oxidation under different conditions give aldehydes and ketones, respectively.

1° alcohols are easily oxidised first to aldehydes and then to acids, 2° alcohols are easily oxidised to ketones, and 3° alcohols are difficult to oxidise because they do not have a H attached to the C carrying the OH group (see Chapter 2).

5.4.2 By Dehydrogenation of Alcohols

This method is suitable for volatile alcohols. Alcohol vapours are passed over heavy metal catalysts (Ag or Cu). 1°, 2°, and 3° alcohols give aldehydes, ketones, and alkenes, respectively (see Chapter 2).

5.4.3 From Hydrocarbons

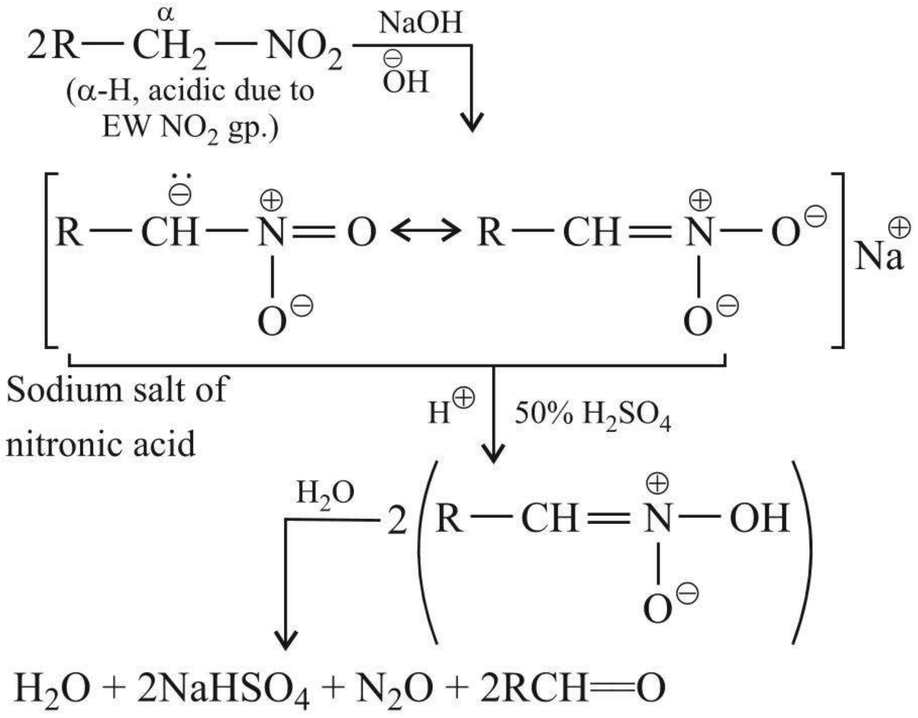
i. **By ozonolysis of alkenes:** Ozonolysis of alkenes followed by reduction with (Zn dust + acetic acid) gives aldehydes or ketones or a mixture of both depending on the substitution pattern of alkene.

ii. **By catalytic hydration of alkynes:** Addition of dil. H_2SO_4 in the presence of $HgSO_4$ to alkyne gives aldehydes or ketones, depending on the nature of alkyne. Ethyne or acetylene gives acetaldehyde, while propyne gives acetone.

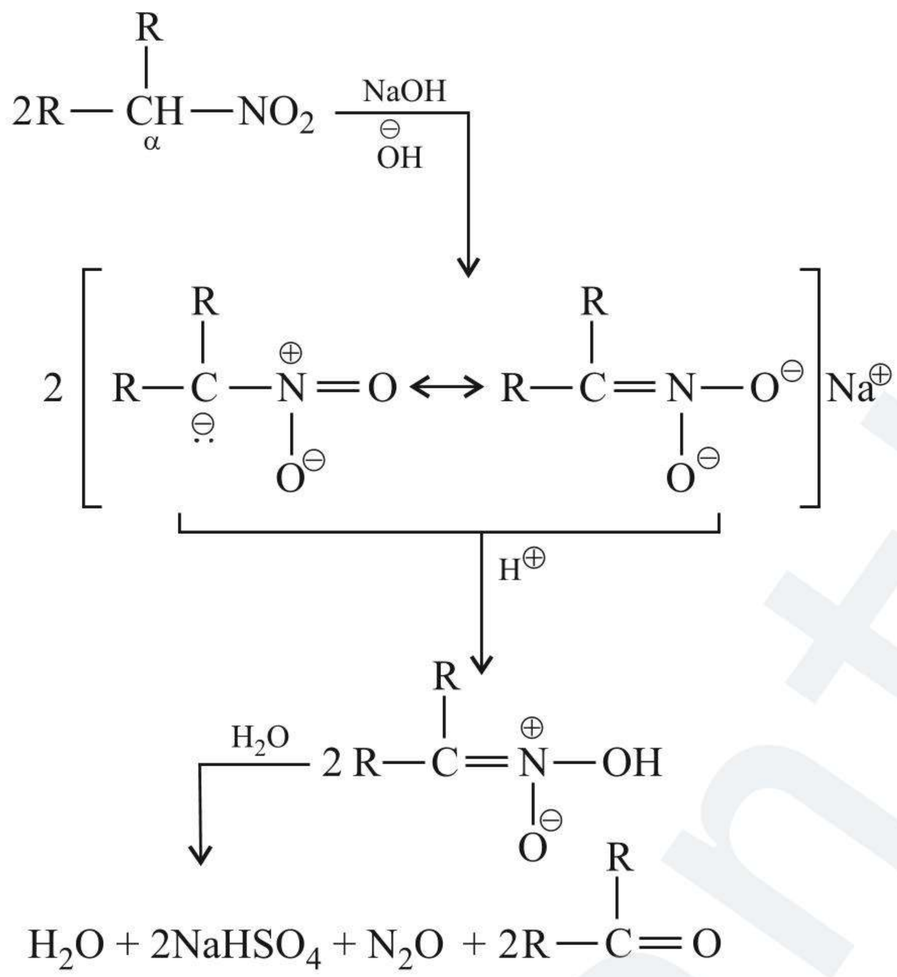
5.4.4 From Nitroalkanes (Nef Carbonyl Synthesis)

When sodium salt of nitronic acid is acidified with 50% H_2SO_4, an aldehyde from 1° nitro compound and ketone from 2° nitro compound are obtained.

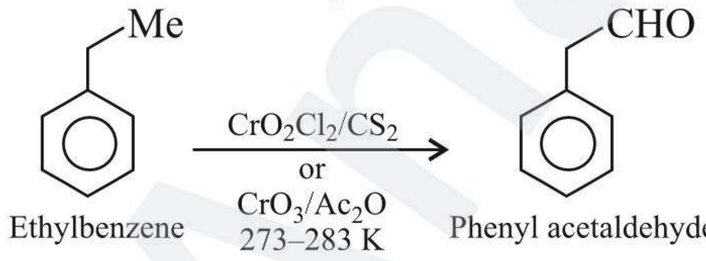
i. 1° RNO_2, containing acidic α-H atom, on reaction with base followed by acidic hydrolysis gives aldehyde.



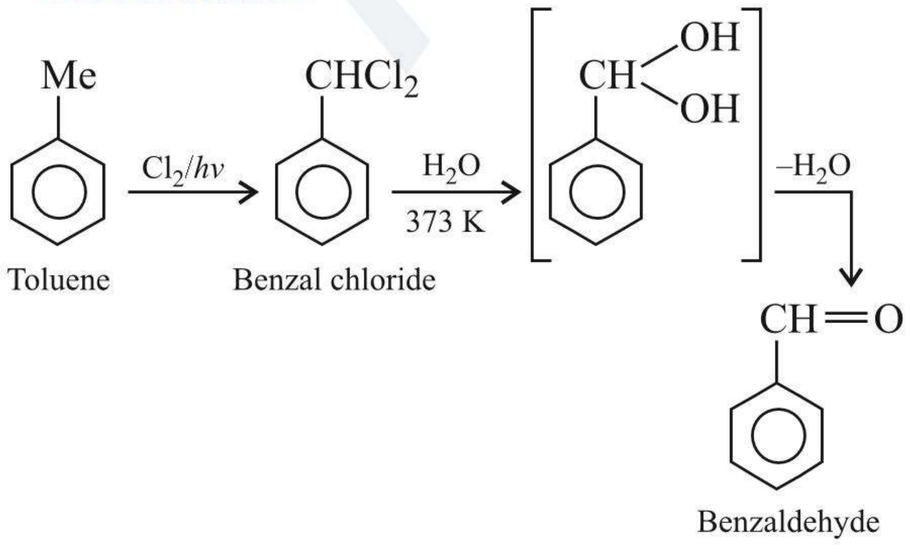
ii. 2° RNO_2, containing acidic α-H atom, under the same conditions gives ketone.



5.4.5 Partial Oxidation of Alkyl Benzene (Etard Reaction)



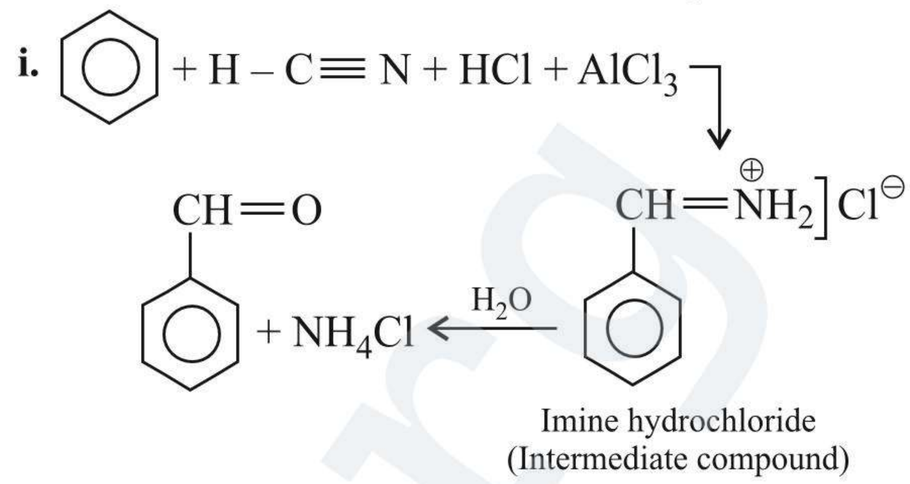
5.4.6 By Side-chain Chlorination Followed by Hydrolysis



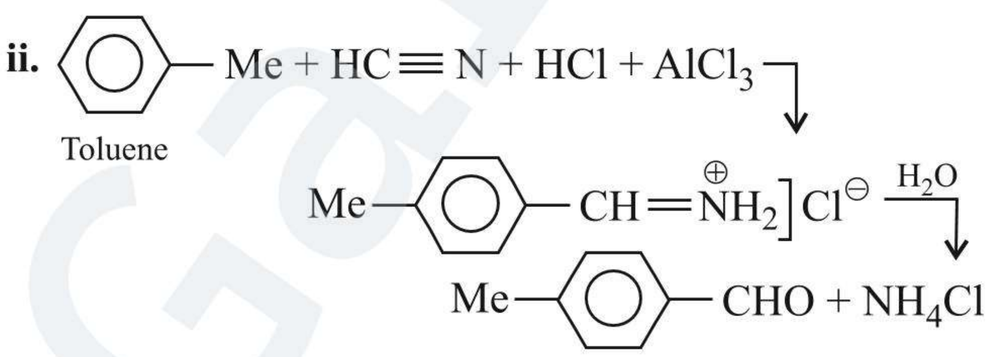
5.4.7 Gattermann Aldehyde Reaction

Benzene or its derivative on reaction with HCN + HCl + $AlCl_3$ gives benzaldehyde or substituted benzaldehyde. Solid $Zn(CN)_2$ is also used as an *in situ* source of HCN, e.g.,

i.



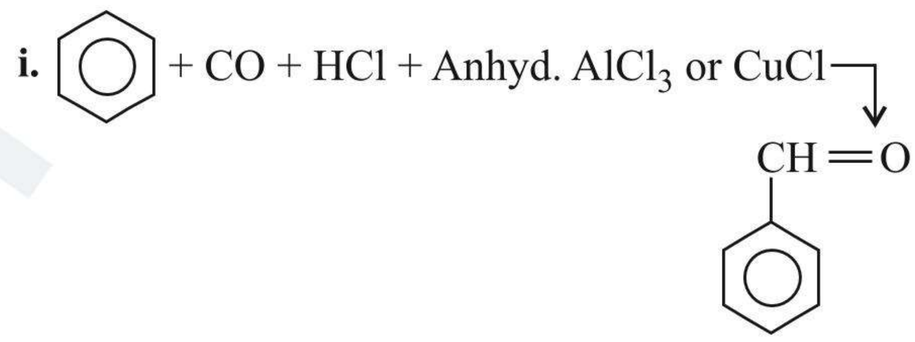
ii.



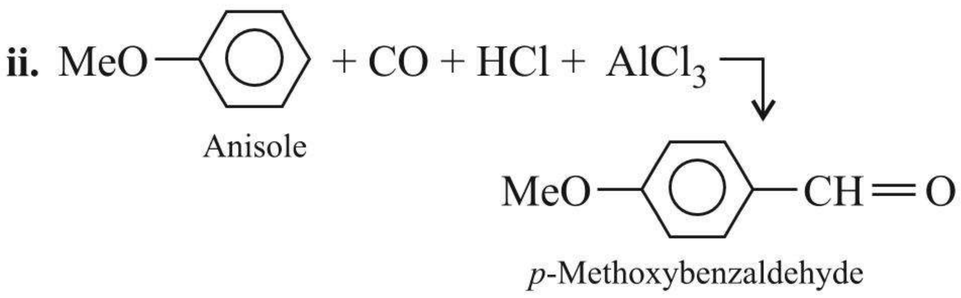
5.4.8 Gattermann–Koch Aldehyde Synthesis

Benzene or its derivative on reaction with (CO + HCl + $AlCl_3$ or CuCl) gives benzaldehyde or substituted benzaldehyde.

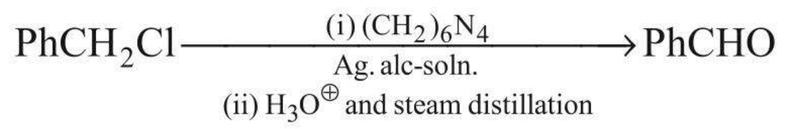
i.



ii.



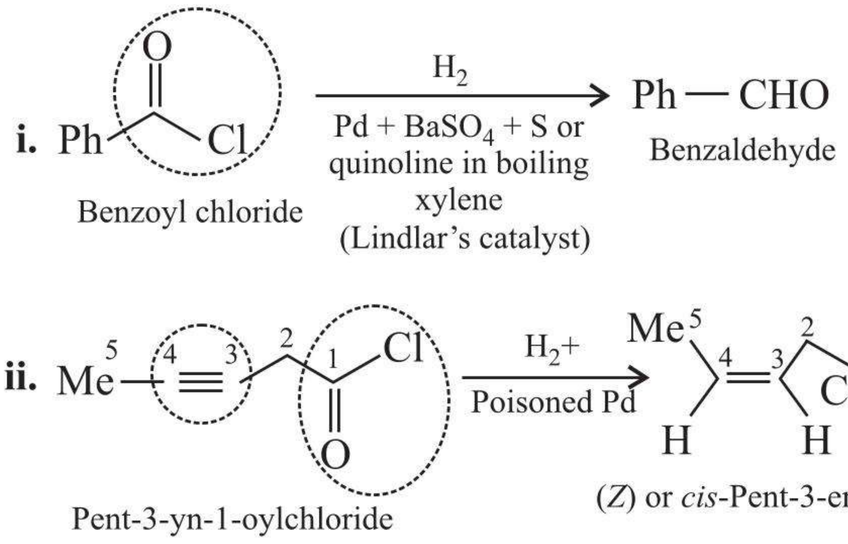
5.4.9 Sommelet's Reaction



5.5 Rosenmund Reduction

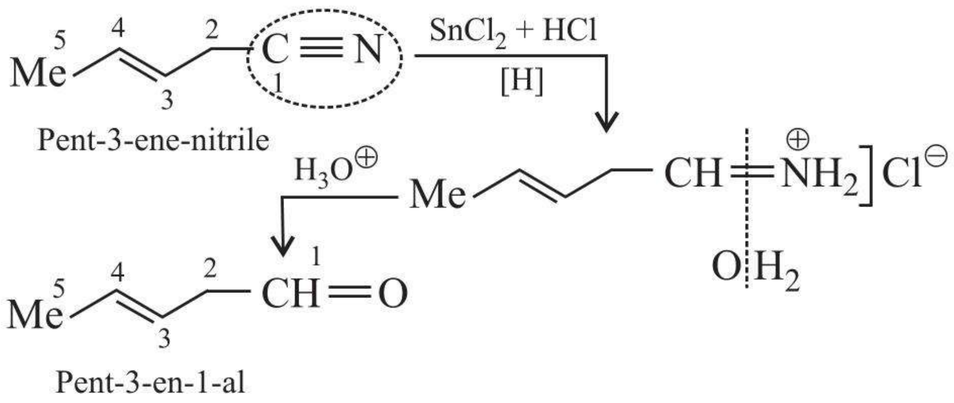
Partial hydrogenation of benzoylchloride with finely divided Pd as catalyst in the presence of $BaSO_4$ and S or quinoline in boiling xylene (as solvent) gives benzaldehyde. This reaction is called Rosenmund reduction. The catalyst under the above condition is called Lindlar's catalyst or poisoned Pd. The Lindlar's catalyst also reduces (C≡C) bond to (C=C) bond in syn-addition.

It is $BaSO_4$ that prevents the aldehyde from being further reduced to alcohols and acts as a poison to the Pd catalyst. Small amount of sulphur and quinoline is very effective in poisoning the calalyst in aldehyde reduction. Moreover, S and quinoline react with small amount of H_2 to give H_2S gas and hydroquinoline, thereby limiting H_2 for further reduction of aldehyde to alcohol. Boiling xylene acts as a solvent.

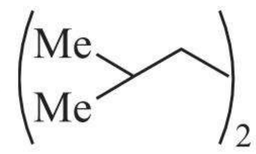


5.6 STEPHEN REDUCTION (PARTIAL REDUCTION OF NITRILES)

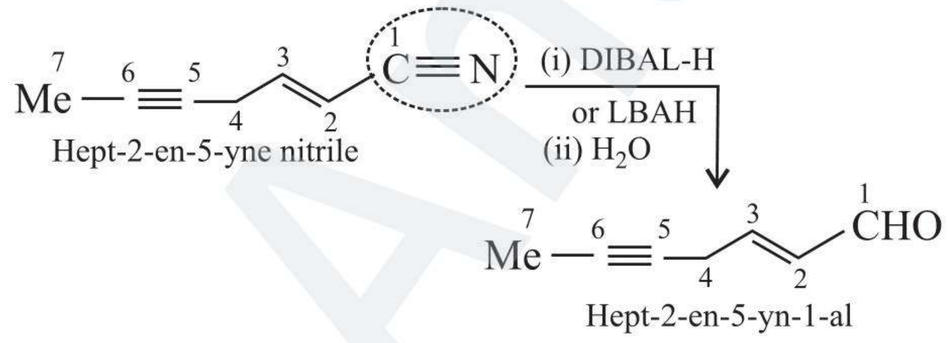
Nitriles (alkyl cyanides) are partially reduced to corresponding imine with $SnCl_2$ (stannous chloride) in the presence of HCl, which on hydrolysis gives corresponding aldehyde. It does not reduce (C═C) or (C≡C) bond. This reaction is called Stephen reduction.



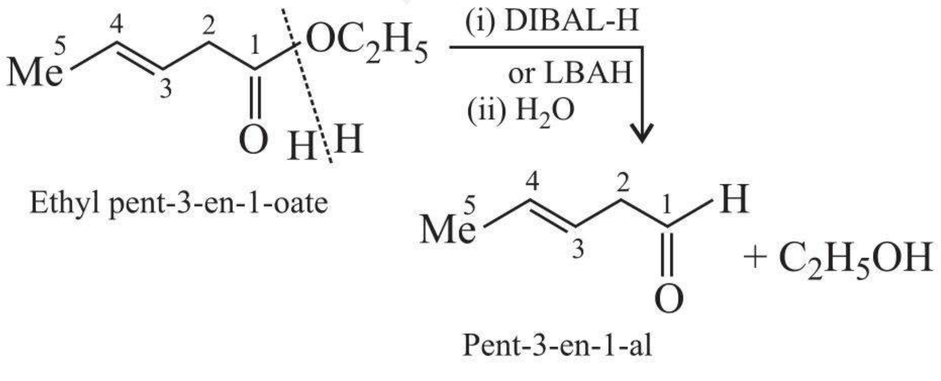
5.7 SELECTIVE REDUCTION OF NITRILES ACID HALIDE AND ESTERS WITH DIBAL-H OR WITH LBAH

Nitriles are partially reduced by (DiBAl-H) or (DBAH) [diisobutyl aluminium hydride  AlH] abbreviated also as $AlH(iBu)_2$, or with LBAH (lithium tri-*t*-butoxy-aluminium hydride [$(Me_3C — O)_3AlH$)] to imines followed by hydrolysis to aldehyde. Both do not reduce (C═C) and (C≡C) bonds. Both are weaker reducing agents than LAH. Reduces acid halides to aldehyde.

i.



ii. Similarly, esters are partially reduced to aldehydes.



iii. $PhCOCl \xrightarrow{DiBAL\text{-}H} PhCHO$

5.8 INDUSTRIAL METHOD FOR THE PREPARATION OF (I) FORMALDEHYDE, (II) ACETALDEHYDE, AND (III) BENZAL-DEHYDE

i. $CH_3OH + O_2 \xrightarrow[Ag]{600°C} CH_2{=}O$

ii. 1. $HC{\equiv}CH \xrightarrow[Hg^{2+}]{Dil.\ H_2SO_4} CH_3{-}CH{=}O$

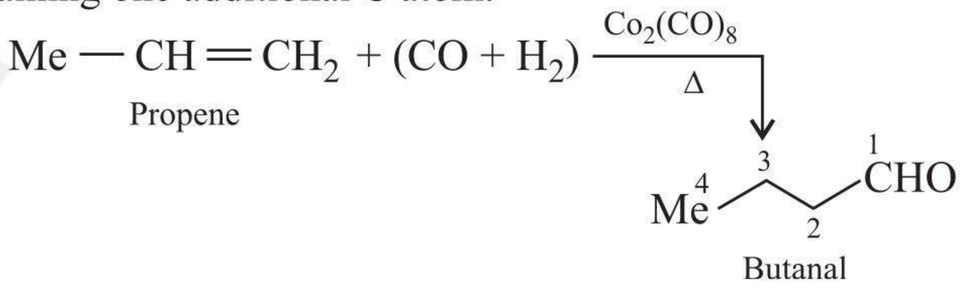
2. Wacker process

$$H_2C{=}CH_2 + O_2 \xrightarrow[H_2O]{PdCl_2,\ CuCl_2} CH_3CHO$$

iii. By side-chain chlorination followed by hydrolysis (see Section 5.4.6).

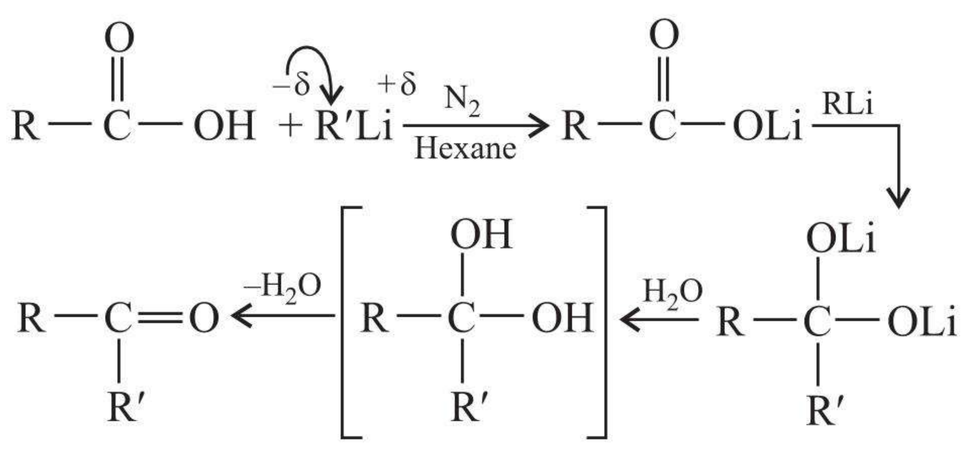
5.9 OXO PROCESS FOR THE PREPARATION OF ALDEHYDE CONTAINING ONE ADDITIONAL C ATOM

Alkenes on reaction with water gas (CO + H_2) in the presence of catalyst $Co_2(CO)_8$ (octacarbonyl dicobalt) give aldehydes containing one additional C atom.

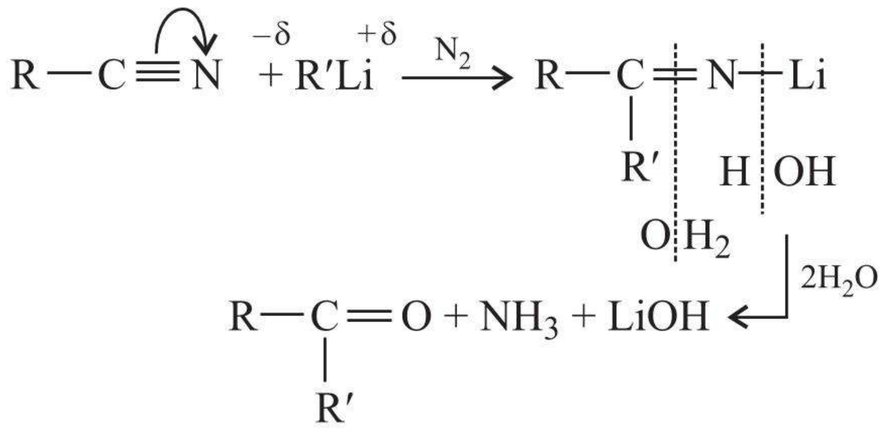


5.10 KETONES FROM CARBOXYLIC ACID

Carboxylic acids (RCOOH) with alkyl lithium followed by hydrolysis give ketones.

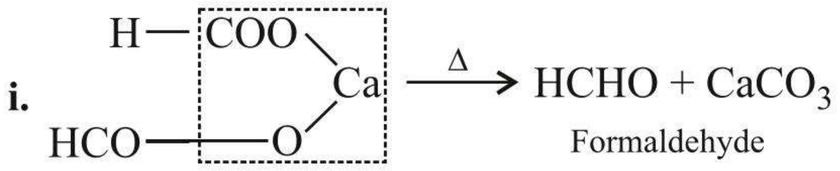


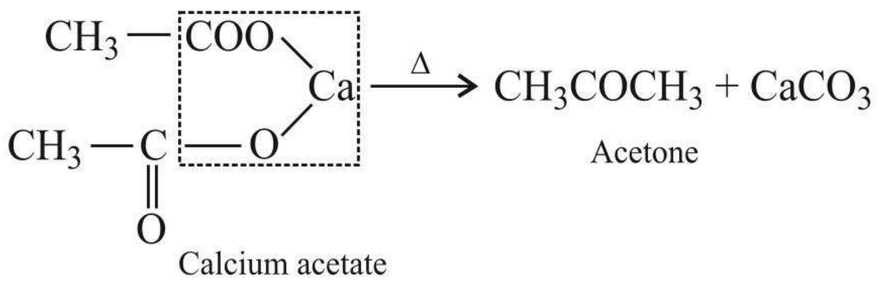
5.11 KETONES FROM ALKYL LITHIUM AND NITRILES

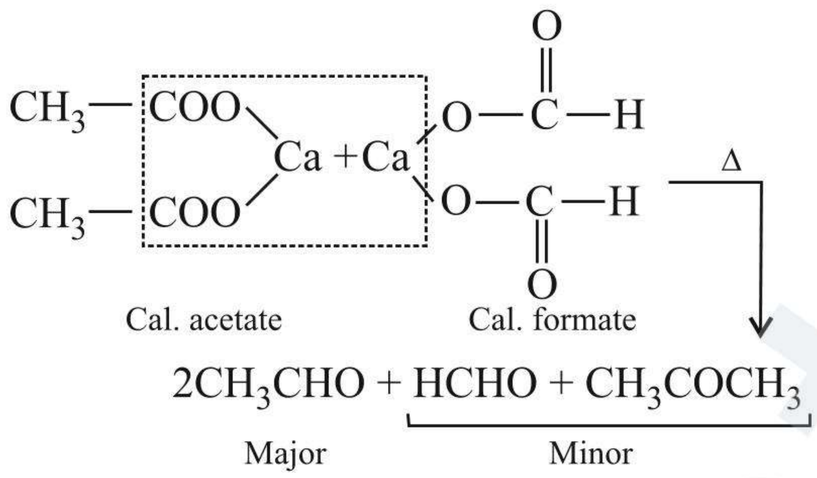


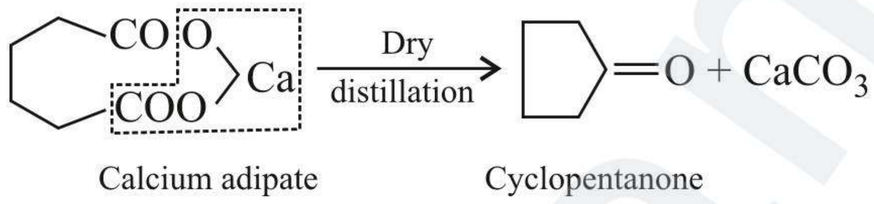
5.12 DRY DISTILLATION OF CALCIUM OR BARIUM SALTS OF FATTY ACIDS

Dry distillation of calcium or barium formate alone gives formaldehyde, while that of calcium or barium salt of any other acid gives ketone. This method is not suitable for the preparation of aldehydes except HCHO, since the yields are low. When a mixture of two salts is heated, three products are formed. For example, dry distillation of a mixture of calcium formate and calcium acetate gives a mixture of HCHO, CH_3CHO, and CH_3COCH_3.

i. 

ii. 

iii. 

iv. 

5.13 BY PASSING THE VAPOURS OF FATTY ACIDS OVER MANGANOUS OXIDE (MnO) AT 573 K

This method is analogous to the above method. Formic acid alone gives formaldehdye; other acids give ketones. Two different acids give mixture of three compounds as in the above case, e.g.,

i. $HCO\boxed{OH + H}\boxed{COO}H \xrightarrow[\Delta]{MnO} HCHO + CO_2 + H_2O$

ii. $CH_3CO\boxed{OH + H}\boxed{COO}H \xrightarrow[\Delta]{MnO}$

CH_3CHO (Major) + HCHO (Minor)
+ CH_3COCH_3 (Minor) + CO_2 + H_2O

iii. $CH_3CO\boxed{OH + H}\boxed{COO}CH_3 \xrightarrow[\Delta]{MnO}$

$CH_3COCH_3 + CO_2 + H_2O$

5.14 FOR SYNTHESIS OF CARBONYL COMPOUNDS FROM DISIAMYL BORANE (Sia_2BH)

For more details, see Chapter 7 (Part 1).

5.15 FOR SYNTHESIS OF ALDEHYDES AND KETONES FROM GRIGNARD REAGENT

For more details on this, refer Chapter 2.

5.16 FOR SYNTHESIS OF KETONES FROM DIALKYL CADMIUM (R_2Cd) AND DIALKYL LITHIUM CUPERATE (R_2CuLi) WITH ACID HALIDES

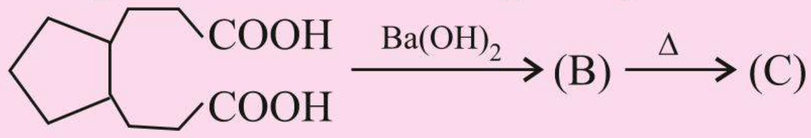
For more details on this, refer Chapter 2.

5.17 FOR SYNTHESIS OF KETONES BY FRIEDEL–CRAFTS ACYLATION REACTION

For more details, see Chapter 3.

ILLUSTRATION 5.3

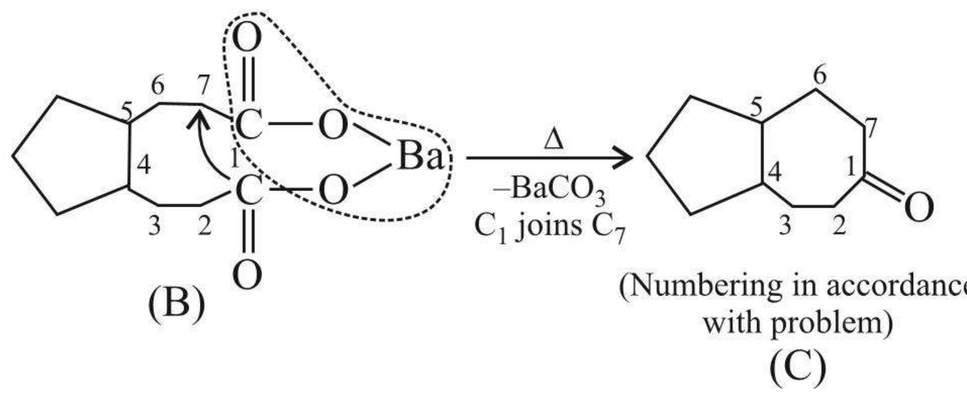
Give the products of the following on dry distillation.

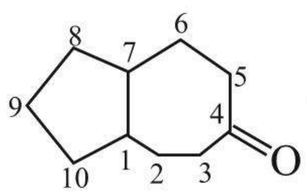
a. 

b. Barium propanoate + Barium acetate

c. Barium benzoate + Barium formate

Sol.

a. 

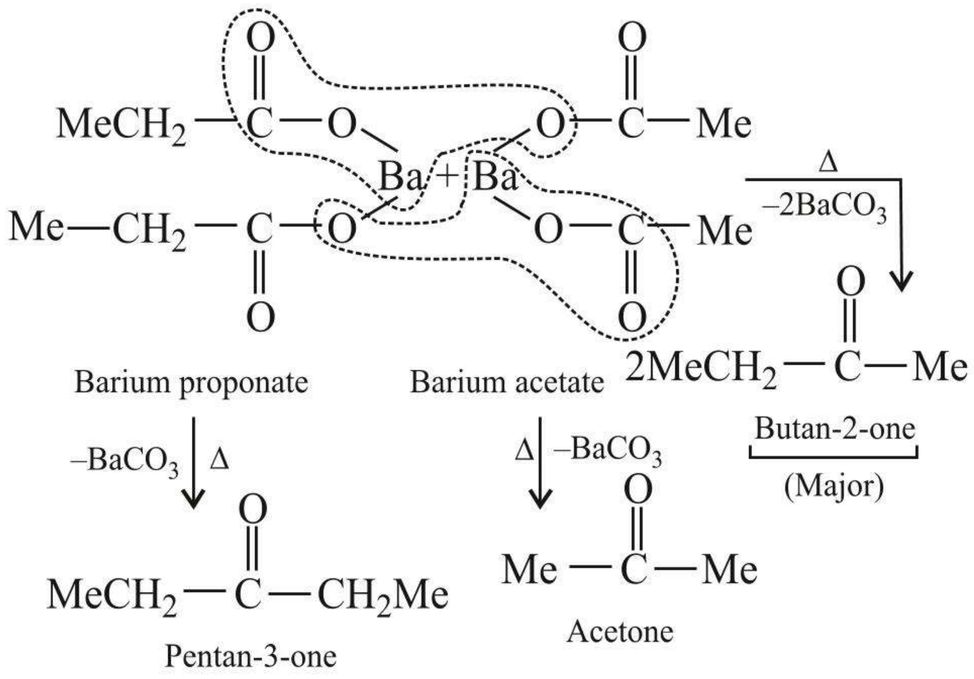


(Bicyclo [5.3.0] decan-4-one)

(C)

Numbering in accordance with naming of the compound.

b.



c.

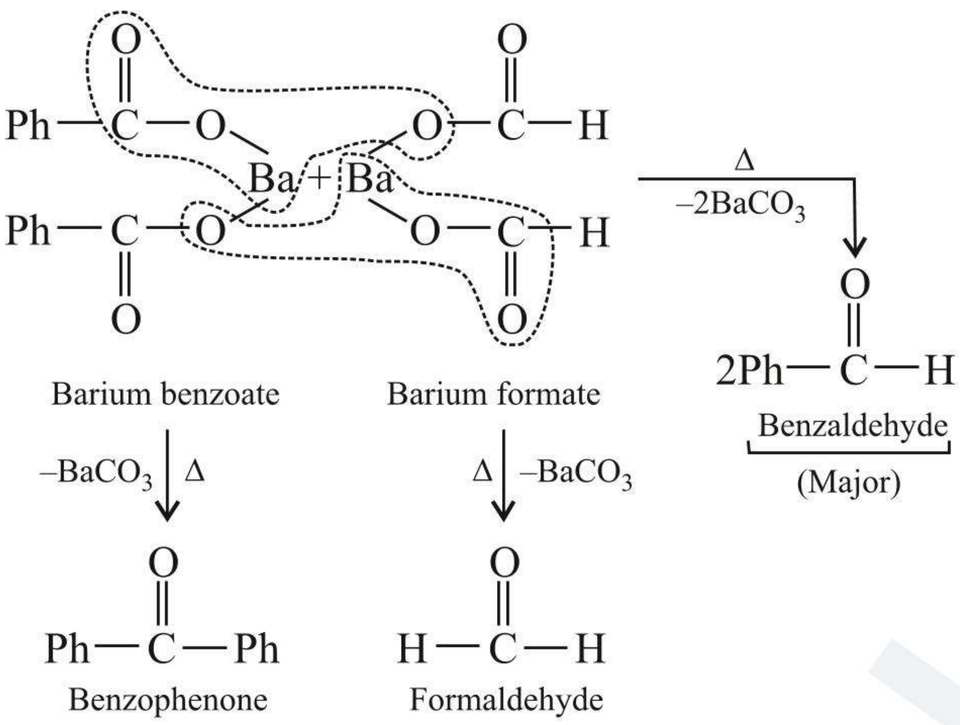
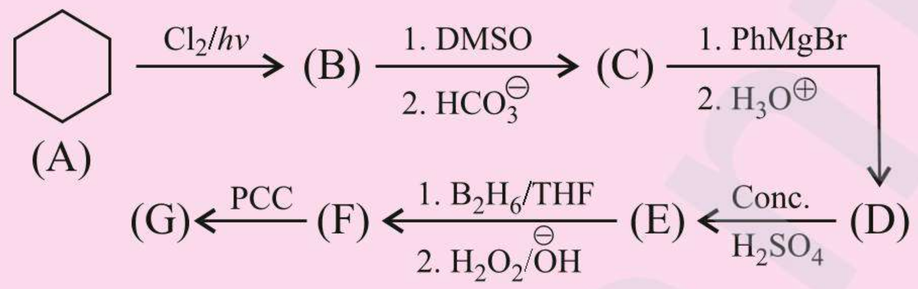


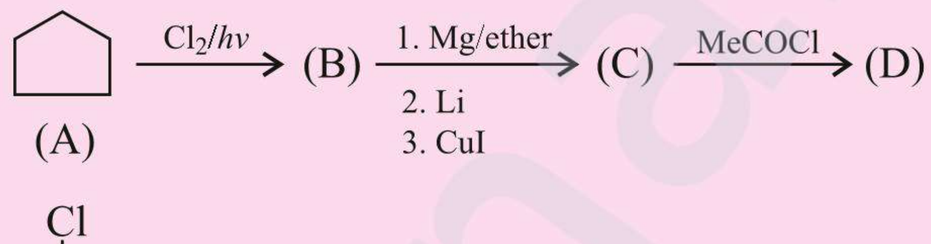
ILLUSTRATION 5.4

Complete the following reactions:

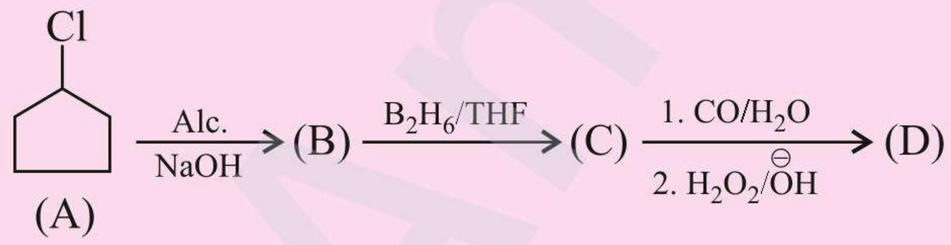
a.



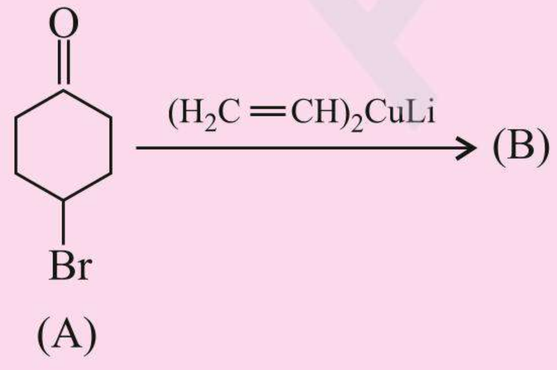
b.



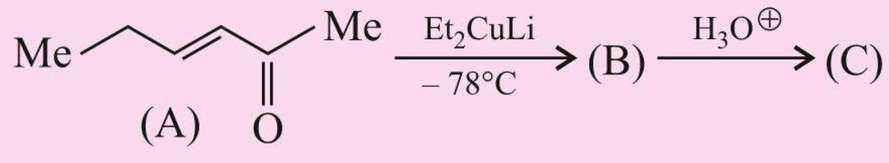
c.



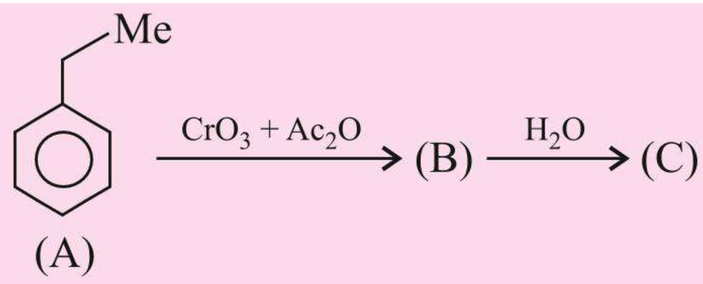
d.



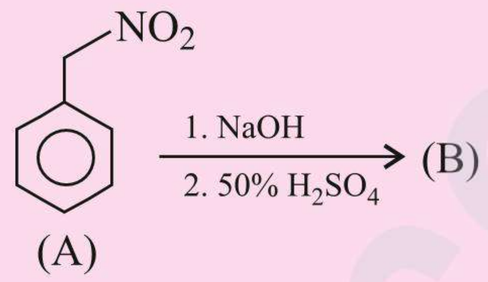
e.



f.

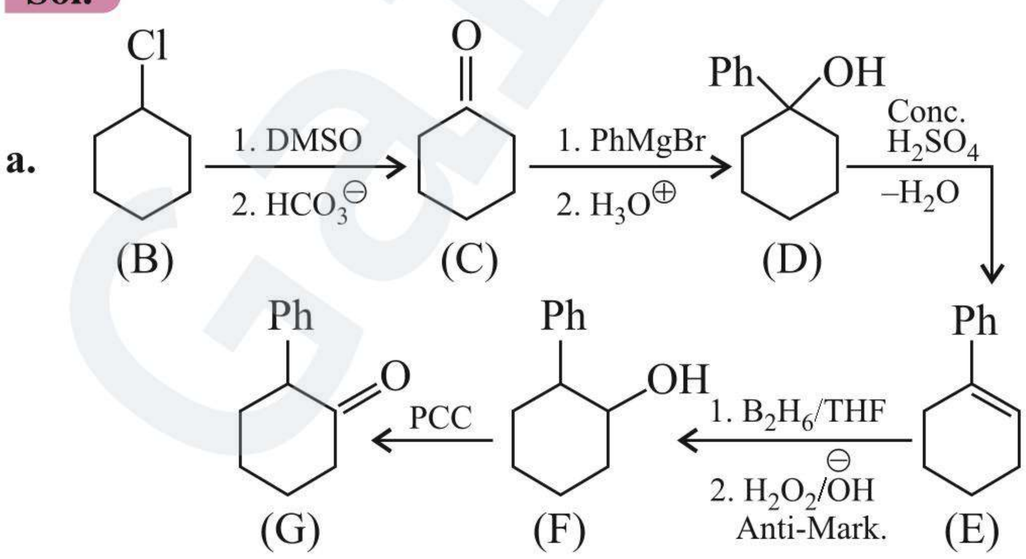


g.

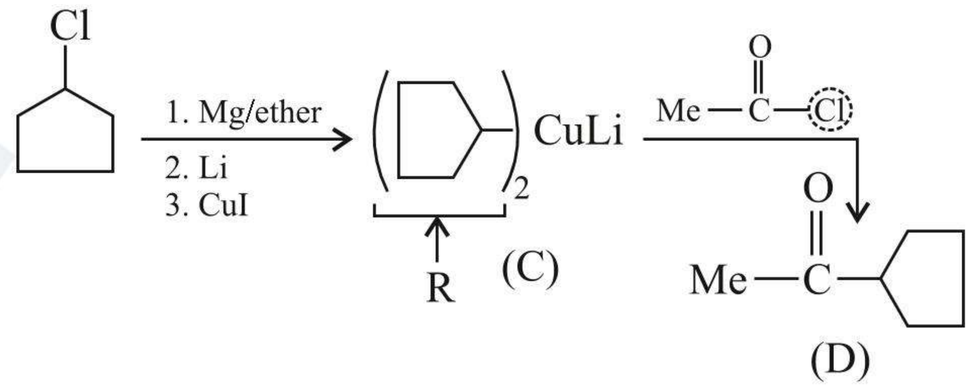


Sol.

a.



b.



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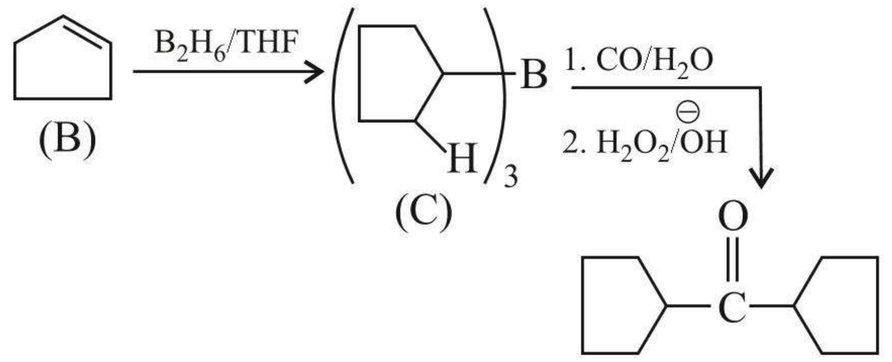
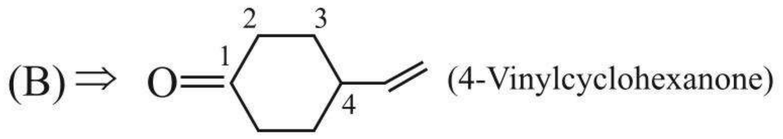
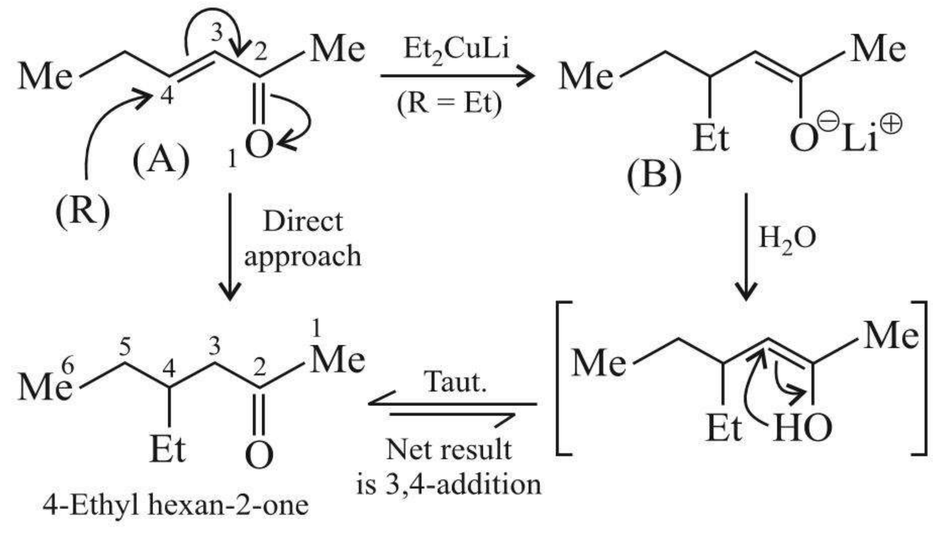


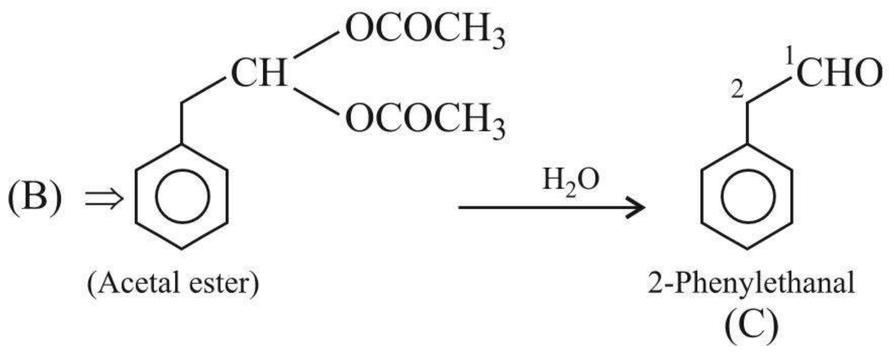
d. R_2CuLi does not add to (C = O) bond but couples.



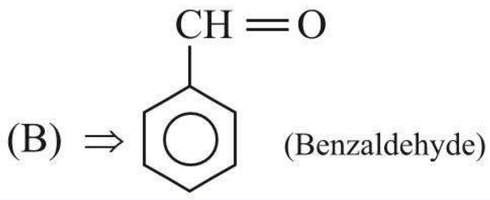
e. This is an example of 1,4-addition or conjugate addition to an α,β-unsaturated carbonyl compound.



f. It is an example of partial oxidation of (CH_3) to (—CHO) (Etard type reaction). Only terminal CH_3 is oxidised to (—CHO).



Formation of acetal ester prevents further oxidation of the intermediate aldehyde to acid (–COOH) group.

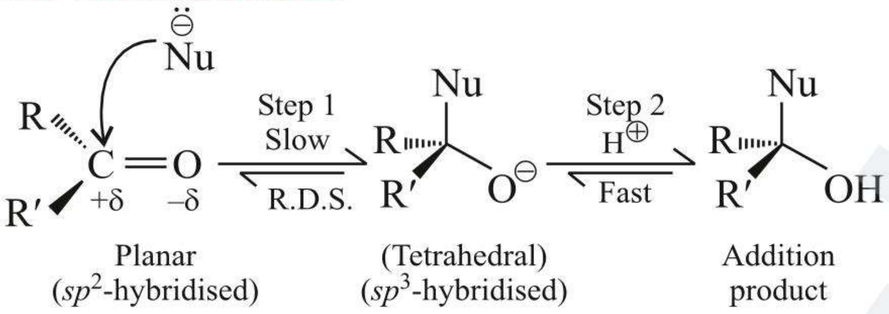
g. 

5.18 CHEMICAL REACTIONS

5.18.1 Nucleophilic Addition (NA) Reactions

Carbonyl compounds undergo nucleophilic addition reaction (–E), whereas alkenes undergo electrophilic addition reaction (+E).

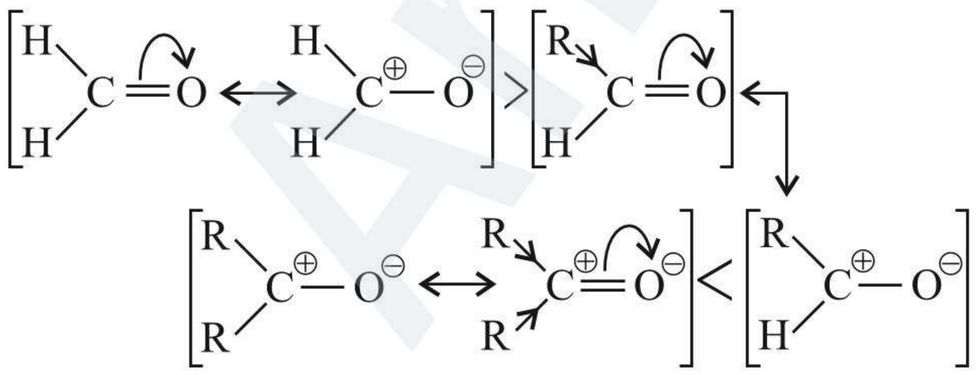
5.18.2 Mechanism



Nucleophile $\left(\ddot{N}u^{\ominus}\right)$ attacks $C^{+\delta}$ atom (electrophilic C atom) of the polar (C═O) group from a direction perpen-dicular to the plane of sp^2-hybridised orbitals of (C═O) group. In this process, there is a change in the hybridisa-tion of C atom, i.e., from sp^2 to sp^3 giving a tetrahedral alkoxide intermediate which takes up $H^{\oplus}$ from the rea-ction medium to give the electrically neutral product with a net result of addition of $Nu^{\ominus}$ and $H^{\oplus}$ on the (C==O) bond.

5.18.3 Reactivity

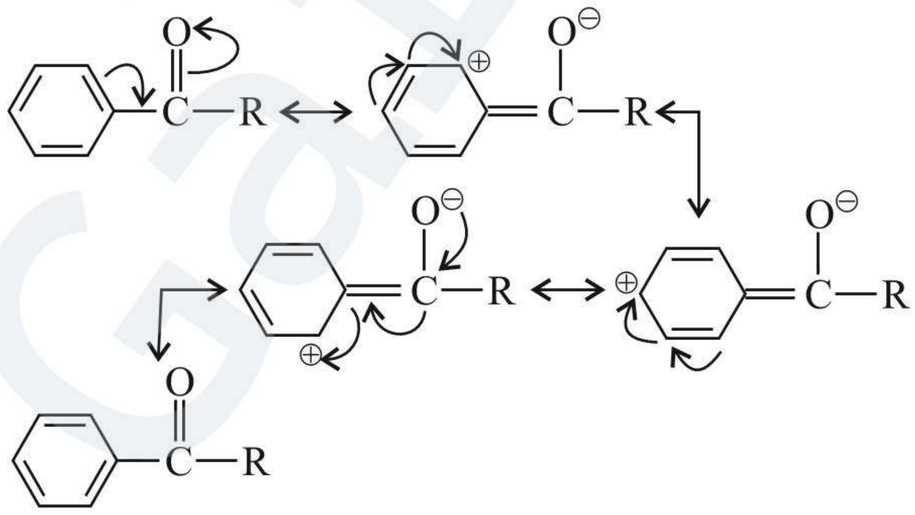
a. Aldehydes are more reactive than ketones towards NA reaction.



Since the alkyl group has $\bar{e}$-donating effect (+I effect), and it will decrease the magnitude of positive charge on the carbonyl group, therefore, reactivity of NA reaction decreases. So, greater the number of alkyl groups attached to the carbonyl group, faster is the positive charge neutralised on C atom of the (C═O) group, and as a result lower is its reactivity towards NA reactions.

Moreover, as the number and size of alkyl groups increase, the attack of nucleophile on carbonyl groups becomes more and more difficult due to steric hindrance (crowding). In other words, as crowding increases, the reactivity decreases accordingly: **HCHO > CH_3CHO > CH_3COCH_3 > $(CH_3)_2CHCOCH(CH_3)_2$ (di-isopropylketone) > $(CH_3)_3CCOC(CH_3)_3$ (di-*tert*-butylketone)**

b. Comparison between aromatic and aliphatic aldehydes and ketones: In general, aromatic aldehydes and ketones are less reactive than the corresponding aliphatic analogues. This is due to dispersal of positive charge of the C atom of (C═O) group into the benzene ring by resonance. Hence, nucleophile attack decreases, as shown:



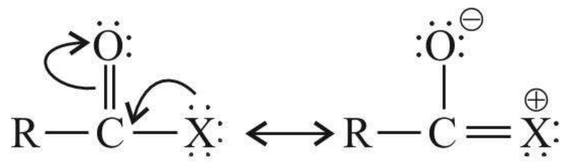
Therefore, PhCHO (Benzaldehyde) > $PhCOCH_3$ (Acetophenone) > PhCOPh (Benzophenone).

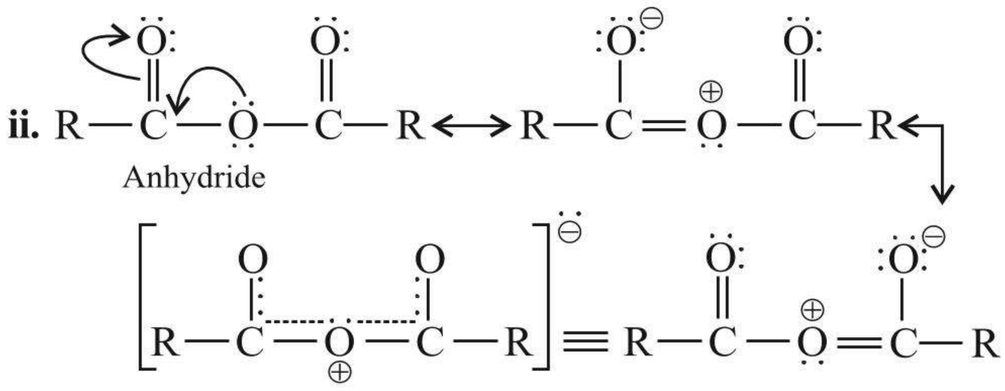
c. Reactivity order:

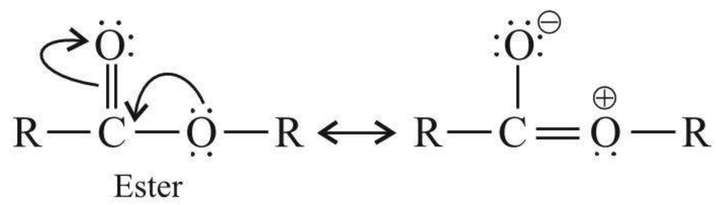
In general, $\bar{e}$-donating group will decrease NA reaction, while $\bar{e}$-withdrawing group increases NA reaction. The order of NA is as follows:

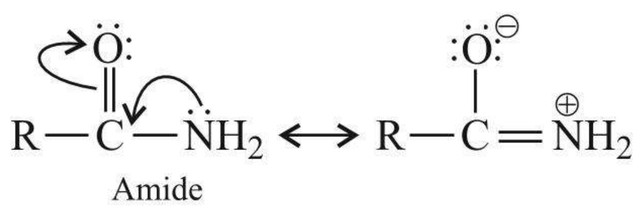
HCHO >Aliphatic aldehyde > Aromatic aldehyde > Aliphatic ketone > Aromatic ketone > Acid halide ($RCOCl < RCOBr < RCOI$) > Azide > Acid anhydride > Ester > Amide > Acid > $RCOO^{\ominus}$.

The NA reactivity order can be explained on the basis of resonance structure and inductive effect of the alkyl groups which is as follows:

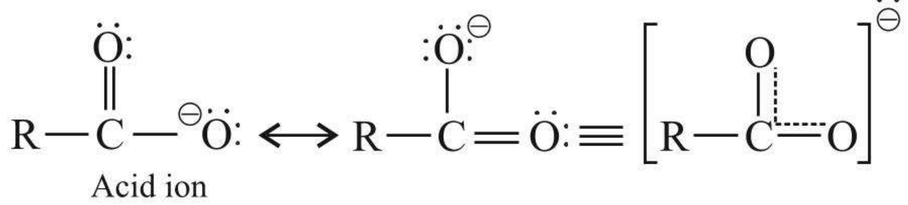
i. 

ii. 

iii. 

iv. 

v. 

vi. 

5.18.4 Order of Reactivity of Acid Derivative with Nucleophile

Reaction of $Nu^{\ominus}$ with acid derivatives is called nucleophilic acyl substitution on the acyl derivatives  . **Order of reactivity with $Nu^{\ominus}$: Acid halide > Anhydride > Ester > Amide.**

5.18.5 Order of Inter-conversion of Acid Derivative (*Trans*-acylation)

Acid halide > Azide > Anhydride > Ester > Amide.

A more reactive derivative may be used to prepare a less reactive derivative by reaction with the appropriate nucleophile. For example, an ester can be prepared from the corresponding acid halide or anhydride, but not from the amide, by reaction with ROH.

Order of reactivity with $Nu^{\ominus}$ and *trans*-acylation is due to the leaving group tendency of the various groups: Weaker the base, better is the leaving group. Leaving group order is: $X^{\ominus} > RCOO^{\ominus} > RO^{\ominus} > NH_2^{\ominus}$.

Leaving group order of halides is: $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$.

Reactivity of acid halide with $Nu^{\ominus}$ and *trans*-acylation:

RCOI > RCOBr > RCOCl > RCOF

Acid strength: HX > RCOOH > ROH > NH_3

Basic strength and nucleophilicity order:

$X^{\ominus} < RCOO^{\ominus} < RO^{\ominus} < NH_2^{\ominus}$

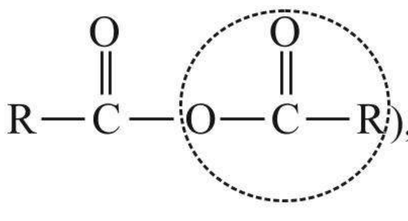
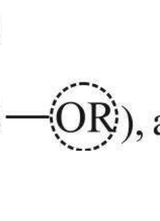
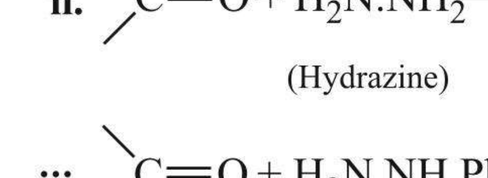
Leaving group order: $X^{\ominus} > RCOO^{\ominus} > RO^{\ominus} > NH_2^{\ominus}$

5.18.6 Order of Hydrolysis

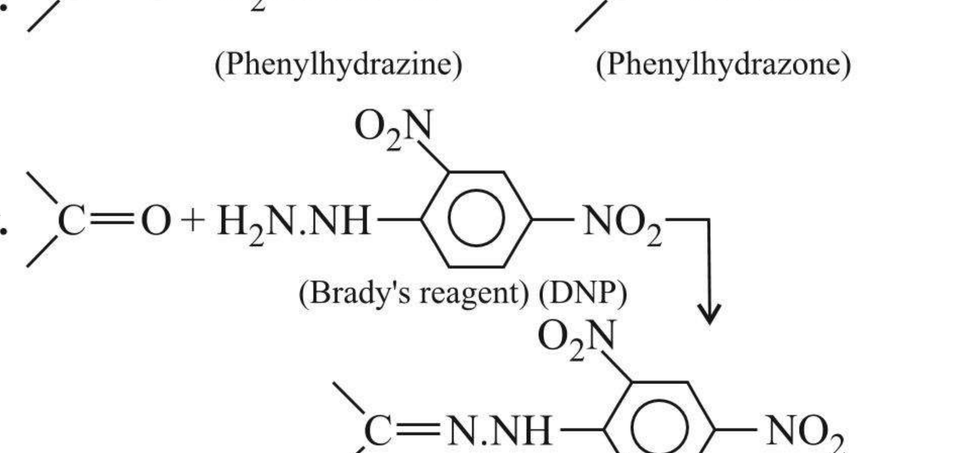
Acid halide > Anhydride > Ester > Amide.

Ease of hydrolysis is again due to the same reason as explained above, i.e., leaving group order of different groups.

5.19 Mechanism of Nucleophilic Acyl Substitution of the Acyl Derivative, 

G represents X  , $RCOO^{\ominus}$ (in anhydride, ), $RO^{\ominus}$ (in ester, ), and $NH_2^{\ominus}$ (in amide, ).

a. In basic solution:



b. In acidic solution:

5.20 Nucleophilic Addition Reaction Followed by Elimination of H_2O- Addition of Ammonia Derivatives

Aldehydes and ketones react with a number of ammonia derivatives such as hydroxylamine (NH_2OH), hydrazine (NH_2NH_2), phenylhydrazine ($PhNHNH_2$), 2,4-dinitro-phenylhydrazine (), and semicarbazide ($NH_2CONHNH_2$) in weakly acidic medium.

i.
(Hydroxylamine) (Oxime)

ii.
(Hydrazine) (Hydrazone)

iii.
(Phenylhydrazine) (Phenylhydrazone)

iv.
(Brady's reagent) (DNP)

2,4-Dinitrophenylhydrazone (DNP derivative)
(Yellow, orange, or red solids).

v. $>C=O + H_2NNHCONH_2$ → $>C=N.NHCONH_2$

(Semicarbazide) (Semicarbazone)

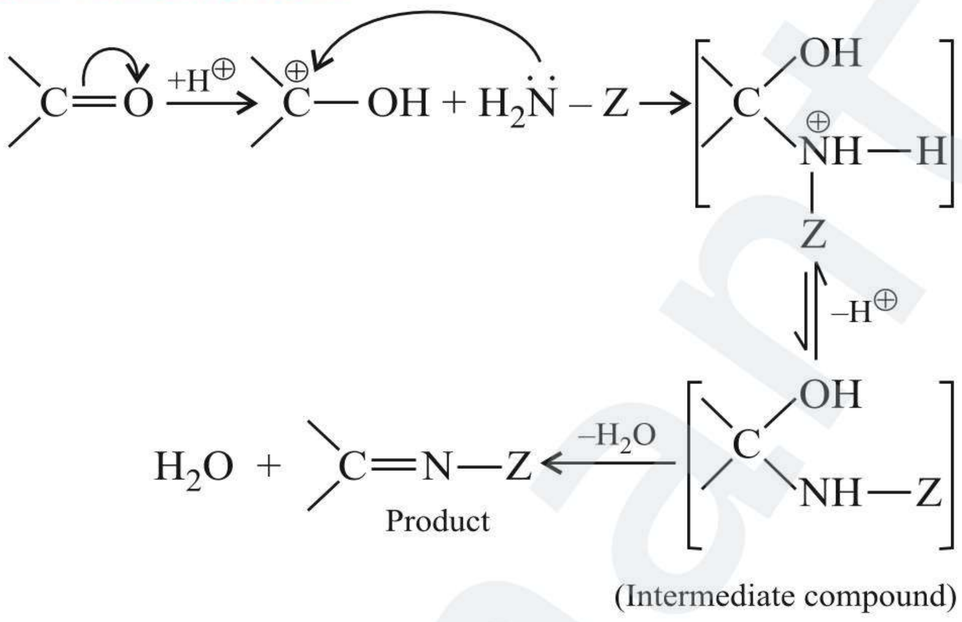
Like NH_3, all these ammonia derivatives are basic and easily oxidised by air. Therefore, these are stored as their salts, hydroxylamine hydrochloride, $NH_2OH.HCl$, etc. Whenever needed for a reaction, the ammonia derivative is generated from the corresponding salt by the action of mild base, sodium acetate.

$$NH_2OH.HCl + CH_3COONa \longrightarrow NH_2OH + CH_3COOH + NaCl$$

The acid thus liberated catalyses the addition reactions. However, the excess of acid should be avoided because the ammonia derivative will form a salt which is no longer nucleophilic in character and hence the reaction will not occur. Therefore, an optimum pH is needed depending upon the basicity of the ammonia derivative and upon the reactivity of the carbonyl compound. Usually, pH in the range of 3–5 is employed.

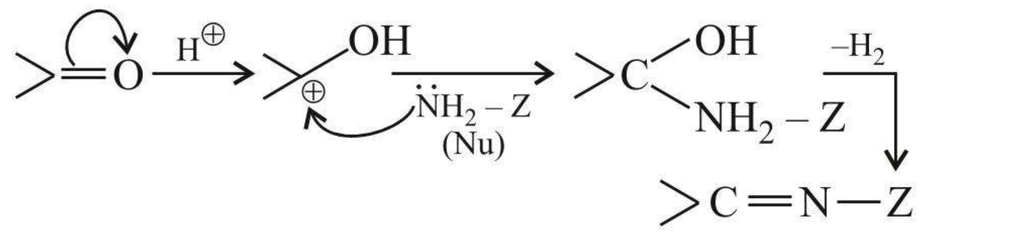
All the above derivatives are crystalline solids with sharp melting points. Therefore, they are used for identification and characterisation of carbonyl compounds. These derivatives can be decomposed with dilute mineral acids to regenerate the original carbonyl compounds. Therefore, these derivatives are also used for the purification of aldehydes and ketones.

5.20.1 Mechanism



Nucleophiles such as NH_3 and their derivatives such as $Z–NH_2$ add to the (C=O) group. The reaction is reversible and catalysed by acid. The equilibrium favours the product formation due to rapid dehydration of the intermediate to form $\left(>C=N—Z\right)$. Dehydration step could be either acid or base catalysed.

During the reaction between carbonyl compounds with ammonia derivatives, a proper pH is maintained. The reason being that to increase positive charge on C of $\left(>C=O\right)$ for the better attack of $Nu^{\ominus}$ centre of ammonia derivative, a small amount of acid ($H^{\oplus}$) is needed.



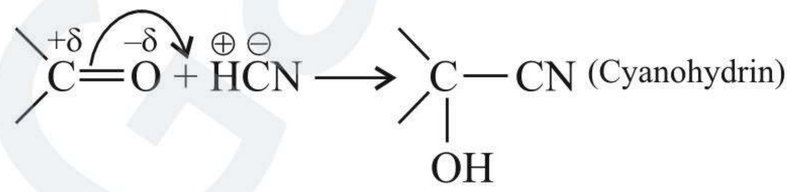
If we add excess of acid (i.e., pH is decreased after a certain limit) ammonia derivative forms its salts and cannot act as nucleophile.

$$\ddot{N}H_2—Z + H^{\oplus} \longrightarrow \overset{\oplus}{N}H_3—Z$$

Therefore, a proper pH ≈ 3 – 5 is required for these reactions.

5.21 SOME IMPORTANT EXAMPLES OF N.A (NUCLEO-PHILIC ADDITION) REACTION

5.21.1 Addition of HCN to Form Cyanohydrin



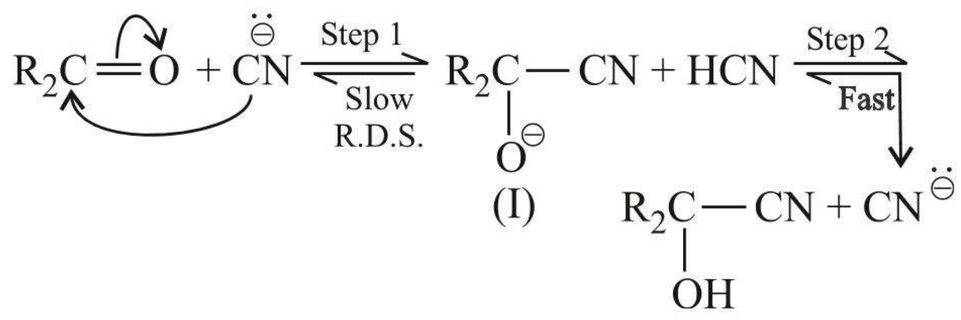
$$CH_3—CH=O + \overset{\oplus\ \ominus}{HCN} \longrightarrow CH_3—CH(CN)(OH)$$

The reaction is carried out in the presence of a base which acts as a catalyst. In the absence of a base, the reaction proceeds extremly slowly.

HCN is generated *in situ* by the addition of mineral acid to a mixture of NaCN and carbonyl compounds. The amount of acid added is insufficient to react with the whole of NaCN added. As a result, the solution remains sufficiently alkaline (due to the hydrolysis of NaCN) to catalyse the addition.

With optimum pH in the range of 9–10, base generates $CN^{\ominus}$ from HCN. If excess base is used, cyanohydrin is decomposed, reversing the equilibrium.

5.21.2 Mechanism



i. If Step 1 is slow and Step 2 is fast, then

$R_1 = K_1 [R_2CO] [CN^{\ominus}]$

ii. If the Step 2 is slow and Step 1 is fast, then

$R_2 = K_2 [I][HCN]$

If the rate is represented by (ii), then Step 1 would be reversible.

$$\therefore \quad K_{eq} = \frac{[I]}{[R_2CO]\,[CN^{\ominus}]}$$

$[I] = K_{eq} [R_2CO] [CN^{\ominus}]$

Substituting [I] in equation (ii), we get

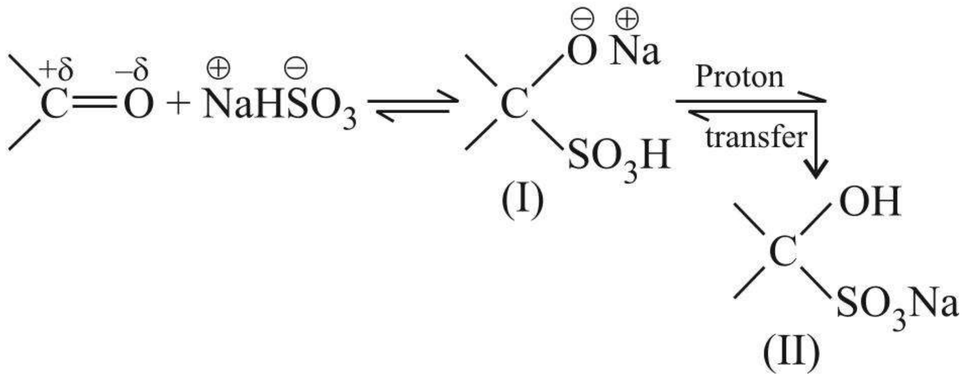
$R_2 = K_2 K_{eq} [R_2CO] [CN^{-}] [HCN]$

$= K_2' [R_2CO][CN^{\ominus}][HCN]$

If rate is represented by (ii), then it would show third-order kinetics and bimolecular. **But the observed rate was found to be (i). Hence, according to equation (i), the reaction is bimolecular and shows second-order kinetics.**

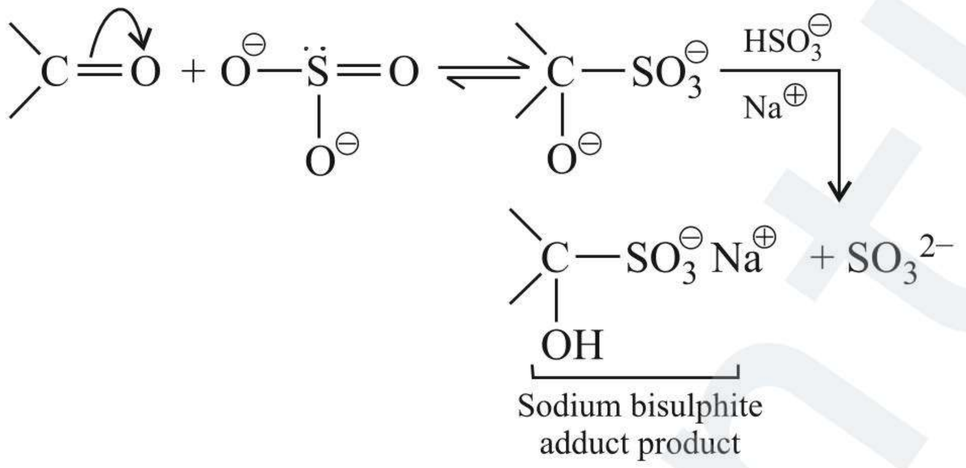
5.21.3 Addition of Sodium Bisulphite

Aldehydes and methyl ketones (ketones containing one (Me) group), when treated with saturated solution of sodium bisulphite solution, add a molecule of sodium bisulphite to form bisulphite addition products. These are crystalline solids and the reaction being reversible, the addition products are decomposed by dilute mineral acids or aq. alkalies to regenerate the original aldehyde or the ketone. Therefore, this reaction is used in the purification and separation of aldehydes and ketones from non-carbonyl compounds. The driving force for the proton transfer from (I) to (II) is the resonance stabilisation of (SO_3^{2-}) group.



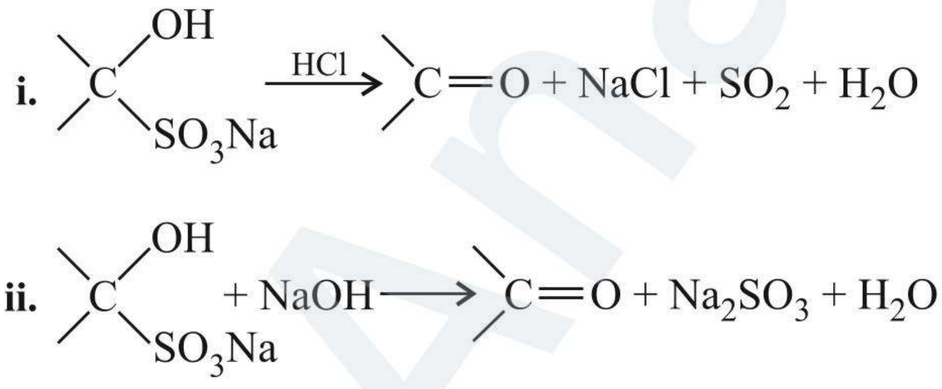
5.21.4 Mechanism

The nucleophile is SO_3^{2-}.



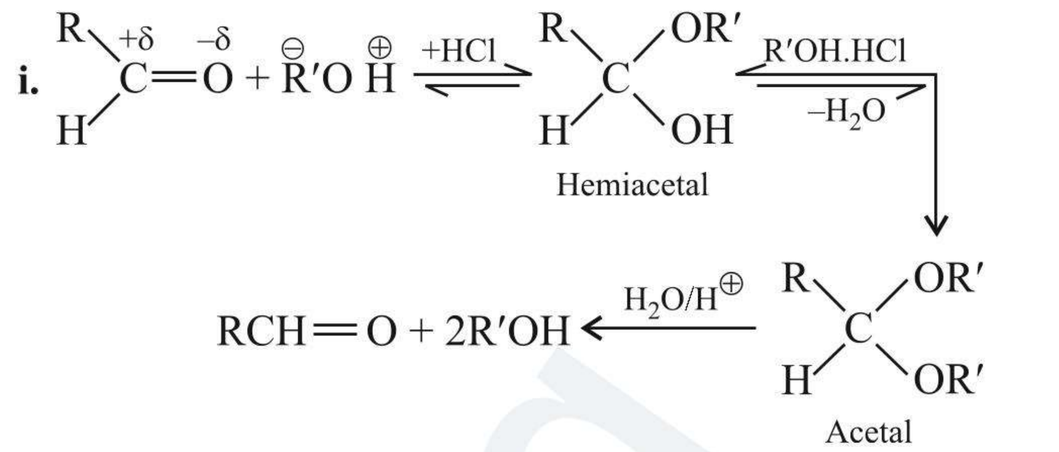
The (C—S) bond is formed rather than (C—O) bond, because S is more nucleophile than O.

Regeneration of carbonyl compound:



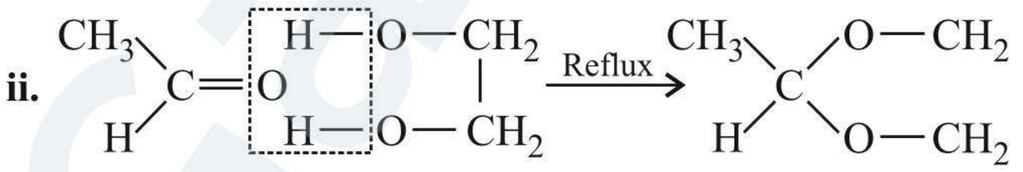
5.21.5 Addition of Alcohols—Acetal and Ketal Formation

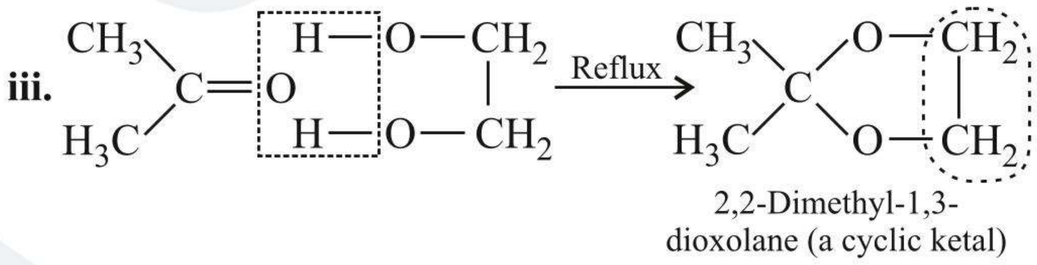
Aldehydes react with alcohols in the presence of dry HCl gas to give gem-dialkoxy compounds known as acetals. A hemiacetal is formed first; it being unstable immediately reacts with another molecule to form stable acetals.



The above reaction is reversible; therefore, acetals can be decomposed by dilute acids to regenerate the aldehyde.

With dihydric alcohols such as ethylene glycol, aldehydes form cyclic acetals, and ketones give cyclic ketals (ketones do not react with monohydric alcohols). This reaction is used to protect (C=O) group.

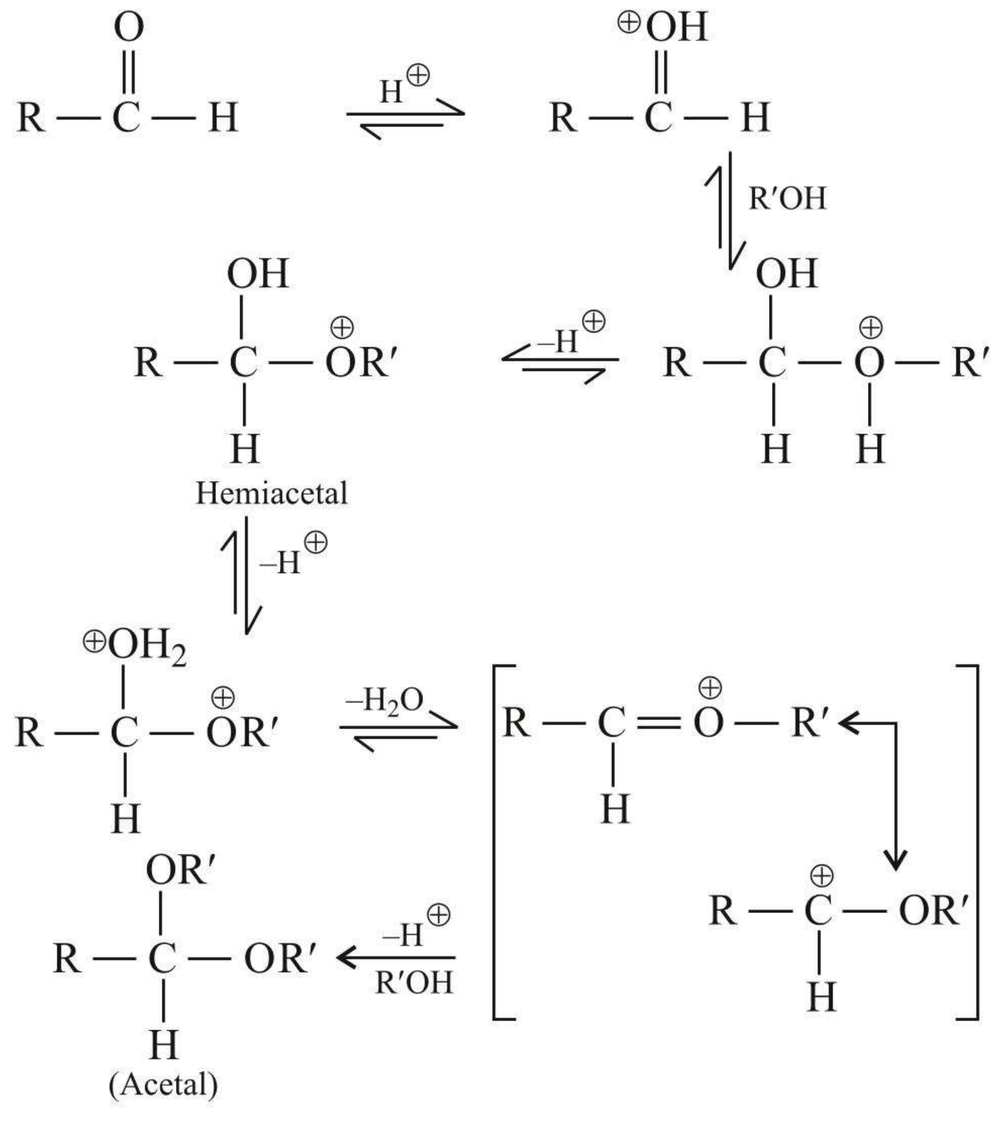




5.21.6 Mechanism of Hemiacetal and Acetal Formation

Rate of hemiacetal formation increases by (i) $H^{\oplus}$ and (ii) $\overset{\ominus}{O}H$. Alcohols are relatively weak nucleophiles and they react slowly to aldehydes and ketones under neutral conditions. In acidic medium, protonation of $O^{-\delta}$ makes more positive charge on the C atom of (C=O) group, making it more reactive.

i. In acidic medium:



The acetal is formed with R′OH in dry HCl and water is distilled off. The acetal is hydrolysed in dilute aqueous acid.

ii. In basic medium:

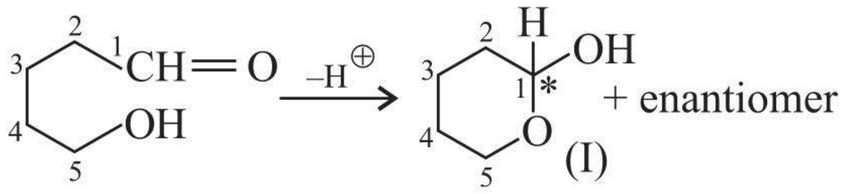
$$ROH + \overset{\ominus}{O}H \rightleftharpoons RO^{\ominus} + H_2O$$

$RO^{\ominus}$ reacts (strong nucleophile) more rapidly with the C atom of (C═O) group than ROH.

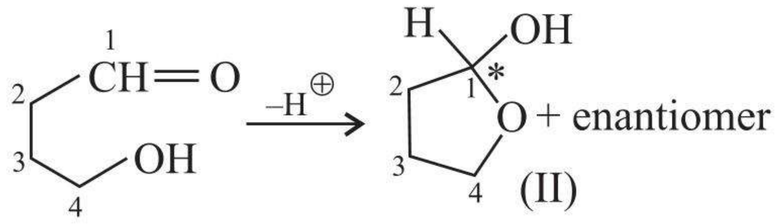
5.21.7 Intramolecular Cyclic Hemiacetal Formation

Hydroxy aldehydes undergo intramolecular reaction in aq. acid to give cyclic hemiacetal.

i.



ii.



Here, (I) is formed faster than (II) and there is more % at equilibrium, since six-membered ring is more stable.

5.21.8 Reaction with NH_3

i. Aldehydes other than formaldehyde react with NH_3 to form aldehyde ammonia adducts. These adducts on heating lose a molecule of H_2O to form aldimines, e.g.,

$$CH_3CH{=}O + \overset{\oplus}{H}{-}\overset{\ominus}{N}H_2 \longrightarrow CH_3CH(OH){-}NH_2$$

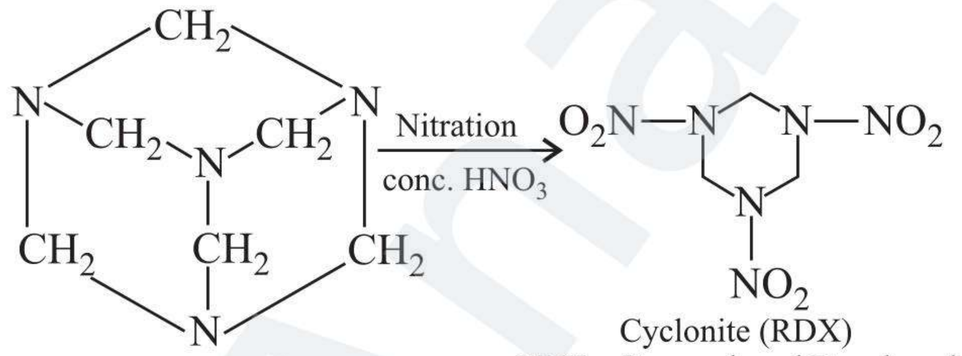
$$CH_3CH{=}NH \xleftarrow[-H_2O]{\Delta}$$

Acetaldimine

ii. Formaldehyde reacts with NH_3 to form hexamethylenetetramine which is used as a urinary antiseptic under the name **Urotropine**.

$$6HCHO + 4NH_3 \longrightarrow (CH_2)_6N_4 + 6H_2O$$

iii.

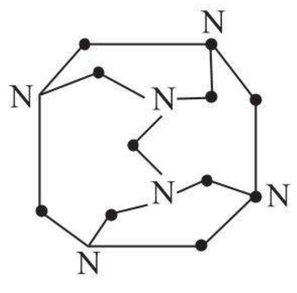


(Urotropine)

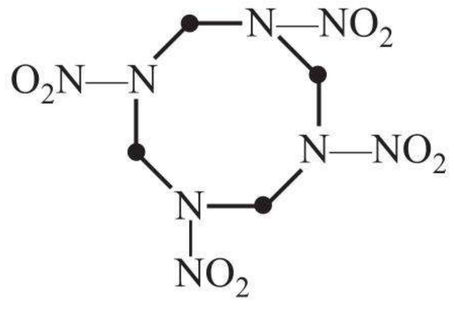
Cyclonite (RDX)
RDX = Research and Developed Explosive

$$9HCHO + 6NH_3 \longrightarrow (CH_2)_9N_6 + 9H_2O$$

Nonamethylene hexamine (I)



(I)



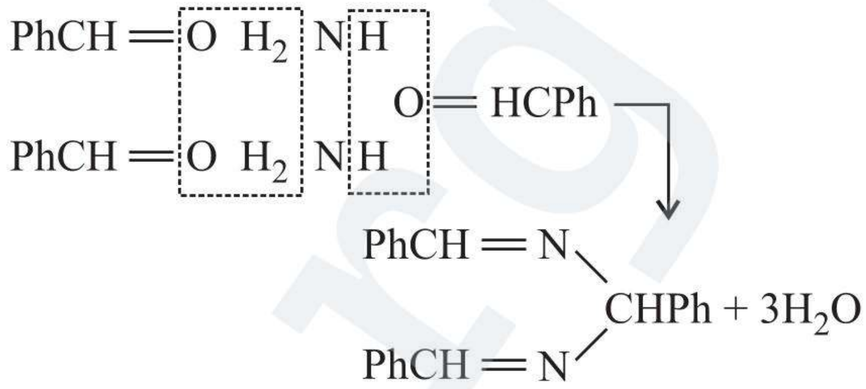
(II)

(I) On nitration gives explosive HMX(II) –Her Majesty Explosive.

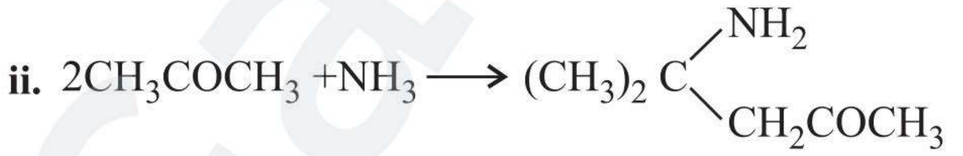
5.21.9 Reaction of PhCHO with NH_3

Unlike aliphatic aldehydes, benzaldehyde reacts with NH_3 to form a complex product called hydrobenzamide. Ketones give complex condensation product with NH_3. Acetone with NH_3 gives diacetonamine.

i.



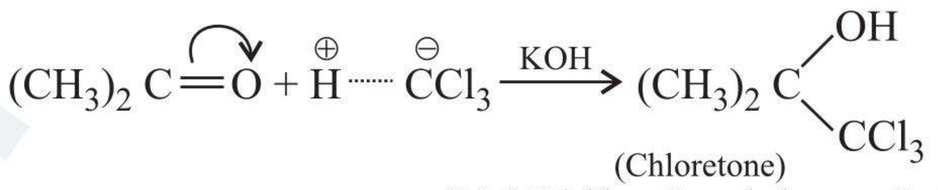
ii.



4-Amino-4-methyl-2-pentanone
(Diacetonamine)

5.21.10 Reaction with Chloroform

Ketones condense with chloroform in the presence of alkali to form addition products, e.g., acetone gives chloretone which is used as a hypnotic (aldehydes do not give this reaction).



(Chloretone)
(1,1,1-Trichloro-2-methylpropan-2-ol)

5.21.11 Reaction with PCl_5

Aldehydes or ketones react with PCl_5 to give gem-dihalides.

i. $CH_3CHO + PCl_5 \longrightarrow CH_3CH(Cl)_2 + POCl_3$

Ethylidene chloride

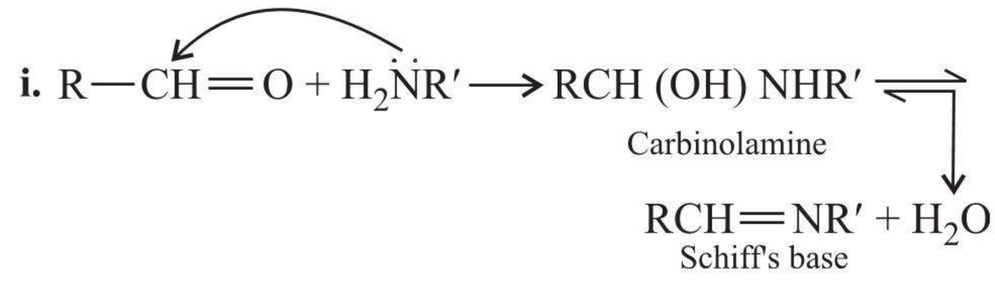
ii. $(CH_3)_2C{=}O + PCl_5 \longrightarrow (CH_3)_2CCl_2 + POCl_3$

2,2-Dichloropropane

5.21.12 Reaction with Primary Amines

Aldehydes and ketones react with 1° amines in the presence of a catalytic amount of an acid to form azomethines or Schiff's bases, e.g.,

i.



ii.

$$PhCHO + H_2N{-}C_6H_5 \xrightarrow{H^{\oplus},\,\Delta} C_6H_5CH{=}NC_6H_5 + H_2O$$

Aniline — Benzalaniline

Illustration 5.5

a. Acid halides, anhydrides, esters and amides, all of them contain (C═O) group but none of them gives test for (C═O) group, i.e., they do not form oximes, hydrazones, and DNP derivatives, etc. Why?

b. Arrange the following in the decreasing order of nucleophilic addition.

i. (1) –CHO (2) $-COCH_3$
(3) –COOH (4) –COCl
(5) $-CONH_2$ (6) $-COOCH_3$
(7) $-COO^{\ominus}$

ii. (1) CH_3CHO (2) CH_3COCH_3
(3) HCHO (4) $C_2H_5CH_2COCH_3$

iii. (1) CH_3COCH_3 (2) $C_6H_5COCH_3$
(3) $C_6H_5COC_6H_5$ (4) $C_6H_5CH_2COCH_3$

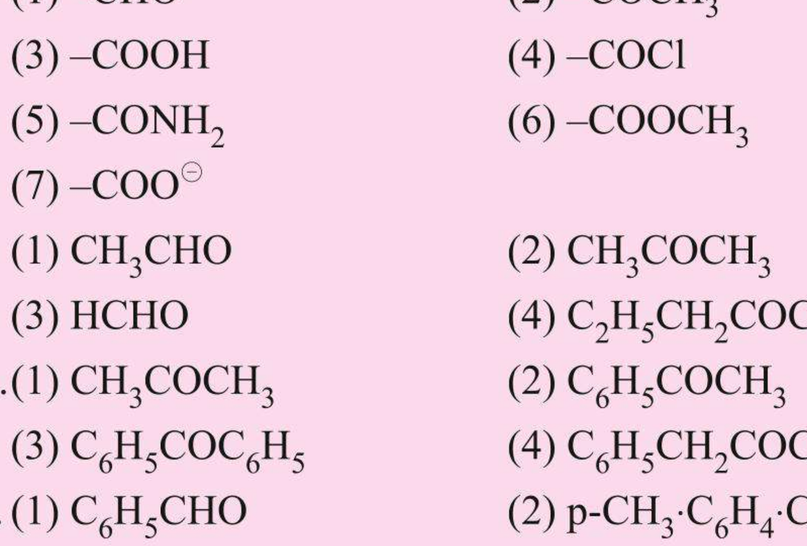
iv. (1) C_6H_5CHO (2) p-$CH_3 \cdot C_6H_4 \cdot CHO$
(3) p-$OH \cdot C_6H_4 \cdot CHO$ (4) p-$NO_2 \cdot C_6H_4 \cdot CHO$
(5) p-$Cl \cdot C_6H_4 \cdot CHO$

v. (1) HCHO (2) CH_3CHO
(3) CH_3COCH_3 (4) Cl_3CCHO

c. Arrange the following in the decreasing order of ease of hydrolysis.

(1) $CH_3COOC_2H_5$ (2) CH_3COCl
(3) $(CH_3CO)_2O$ (4) CH_3CONH_2

d. Arrange the following in the decreasing order of ease of acid-catalysed esterification of:

i. 
(1) (2) (3)

ii. (1) CH_3CH_2COOH (2) $(CH_3)_2CHCOOH$
(3) $(CH_3)_3CCOOH$

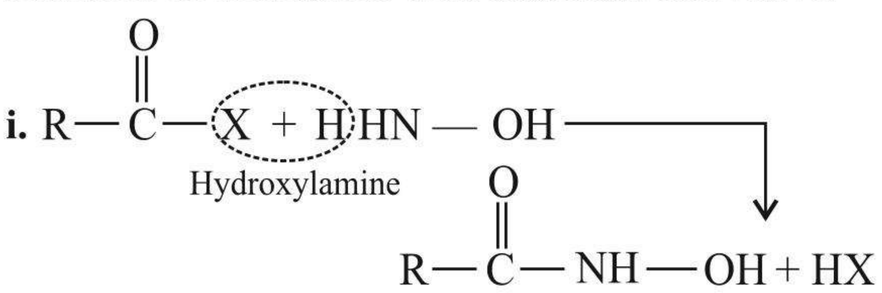
iii. (1) $CH_3CH_2CH_2OH$ (2) $CH_3CHOHC_2H_5$
(3) $(CH_3)_2C(OH)C_2H_5$

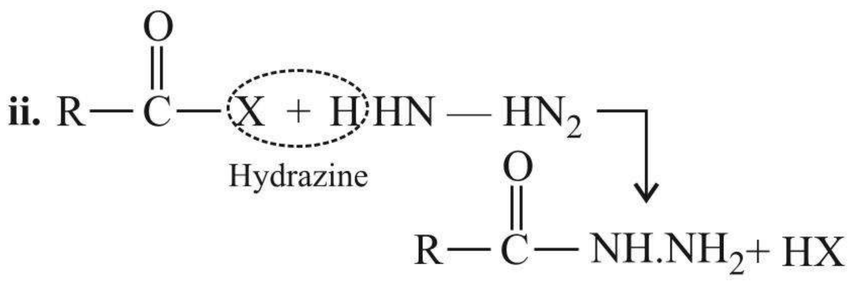
Sol.

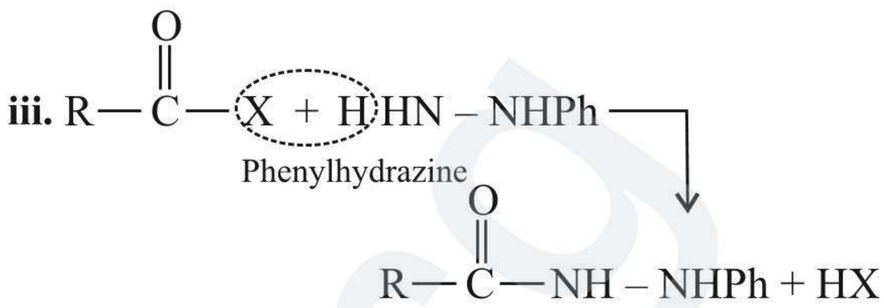
a. All the compounds do not contain a true (C═O) bond as shown by their resonance structures and hence do not give any test of (C═O) group.

However, all the acid derivatives react differently (nucleophilic acyl substitution) with ammonia derivatives e.g.,

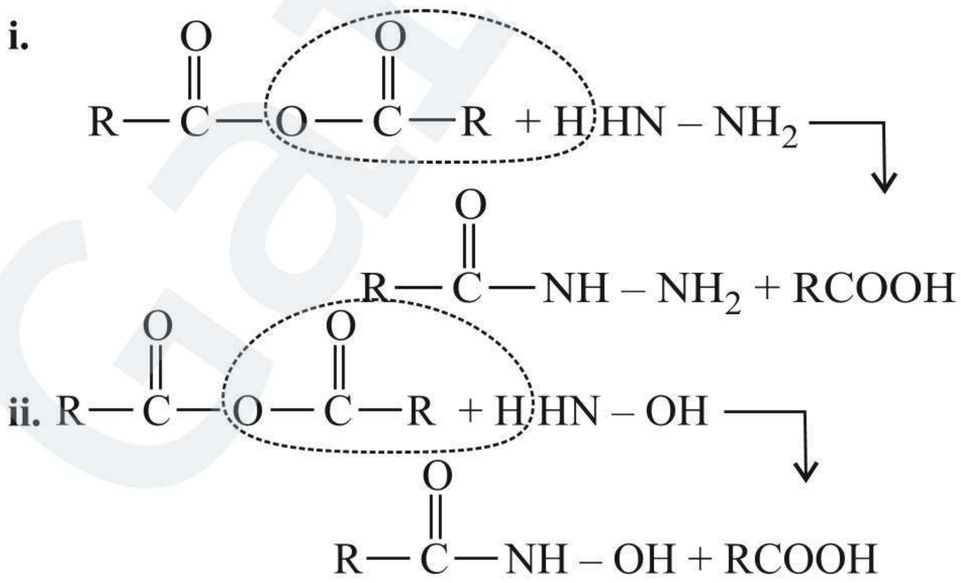
I. Reaction of acid halide with ammonia derivative:



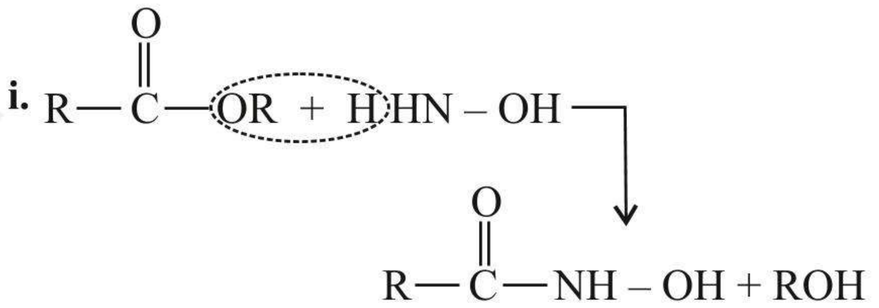




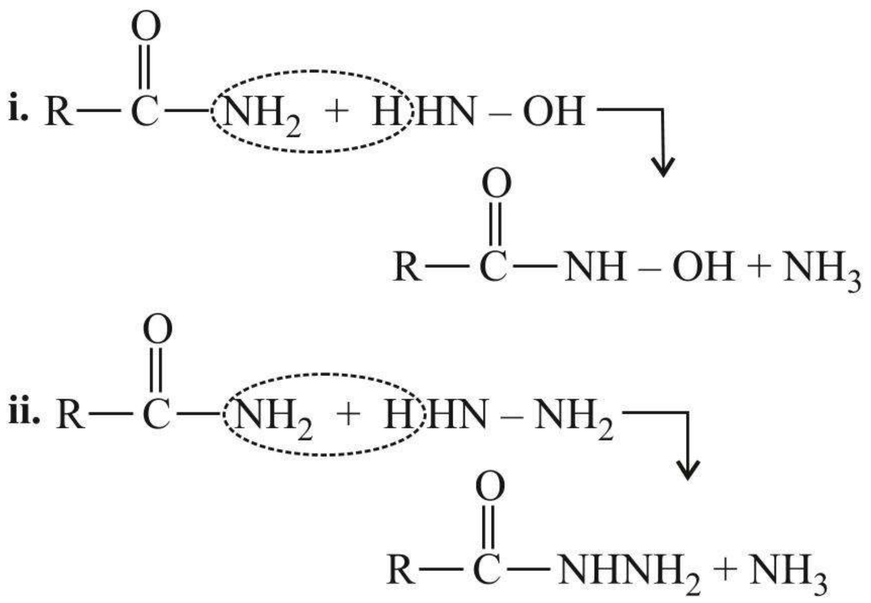
II. Reaction of anhydride with ammonia derivative:



III. Reaction of esters with ammonia derivative:



IV. Reaction of amide with ammonia derivative:

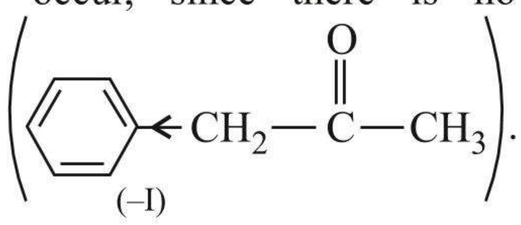


b. i. 1 > 2 > 4 > 6 > 5 > 3 > 7 (Aldehyde > Ketone > Acid chloride > Ester > Amide > Acid > Acid ion)

ii. 3 > 1 > 2 > 4

iii. 4 > 1 > 2 > 3

More the $\bar{e}$-withdrawing group, faster is the NA. In (4), Ph group is $\bar{e}$-withdrawing by –I effect

(+R cannot occur, since there is no extended conjugation) 

iv. 4 > 5 > 1 > 2 > 3
[*p*-NO_2—(–I and –R), *p*-Cl (–I) > Standard > *p*-Me (+I and H.C.) > *p*-OH (+R and –I)]

v. 4 > 1 > 2 > 3 [(Cl_3C—CHO) (–I of 3Cl) > HCHO > CH_3CHO > CH_3COCH_3]

c. 2 > 3 > 1 > 4 (Acid chloride > Anhydride > Ester > Amide)

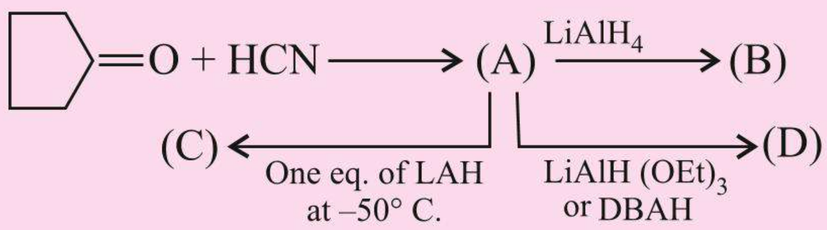
d. As the size of substituents on the α-C increases, the tetrahedrally bonded intermediate becomes more crowded. Greater the crowding, slower is the reaction.

i. 1 > 2 > 3 **ii.** 1 > 2 > 3 **iii.** 1 > 2 > 3

Illustration 5.6

a. $MeCHO + HCN \rightarrow A \xrightarrow{HOH/H^{\oplus}} B \xrightarrow[Heat]{H_2SO_4} C$

$C \xrightarrow[2.\ H_2O_2/\overset{\ominus}{O}H]{1.\ BH_3/THF} (D)$

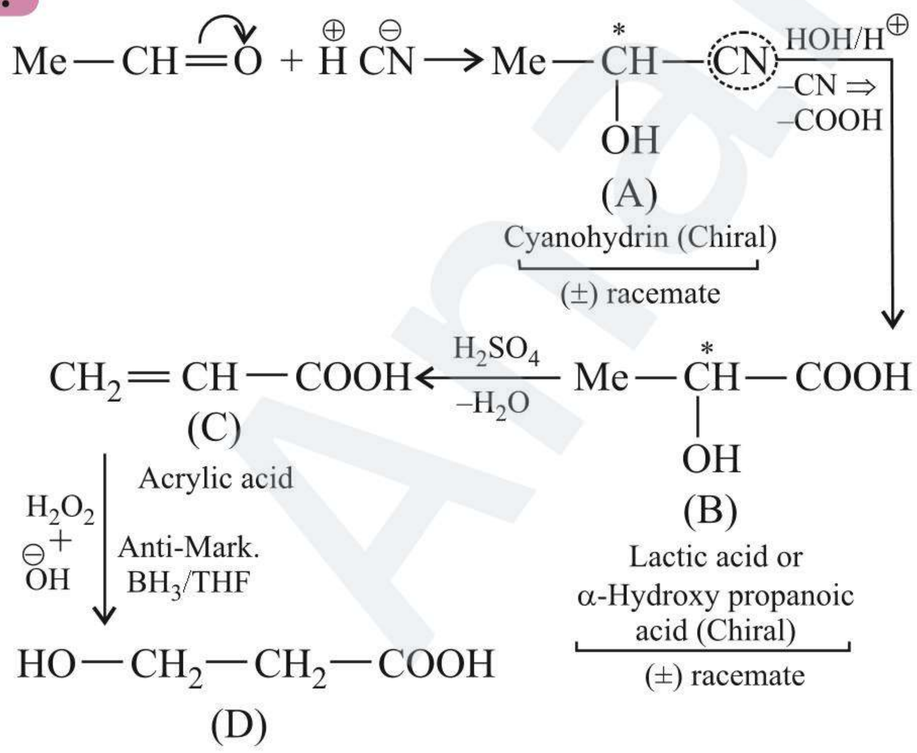
b. 

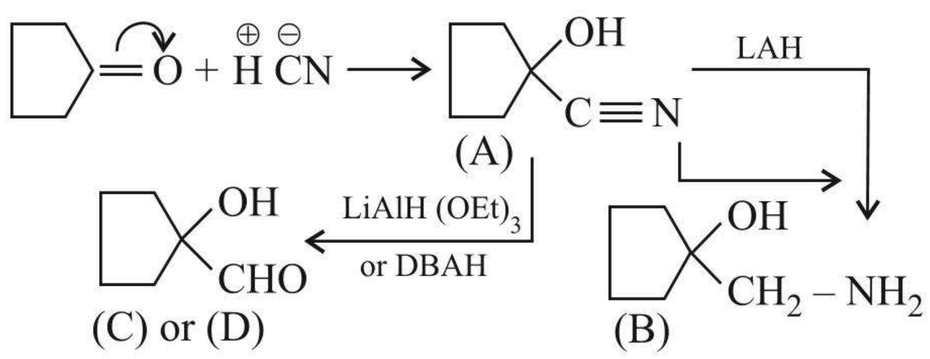
c. Acetone on reaction with NH_2OH gives one compound, whereas acetaldehyde gives two compounds that can be separated. Why?

d. Acetone on reaction with HCN gives one compound, whereas acetaldehyde gives two compounds that are difficult to separate. Why?

e. Butan-2-one gives sodium bisulphite addition product, whereas pentan-3-one does not. Why? (Test to differentiate Butan-2-one and pentan-3-one)

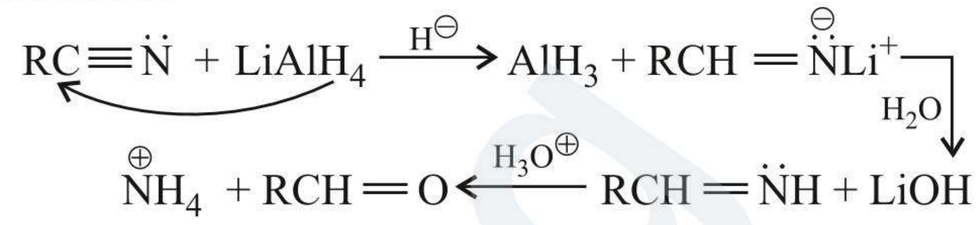
Sol.

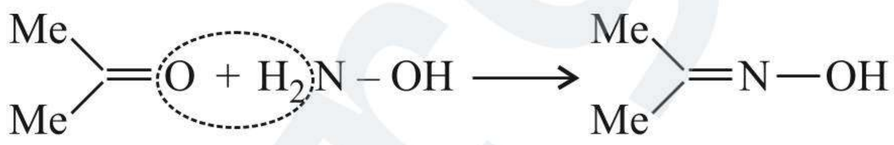
a. 

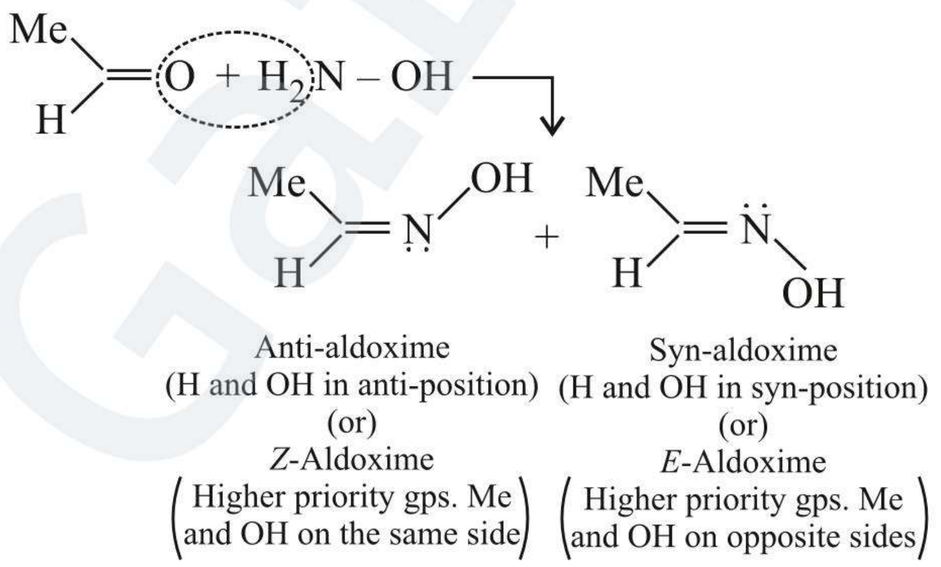
b. 

With one equivalent of LAH at low temperature, the reaction can be used to avoid over-reduction and proceed only upto aldehyde stage. Deactivated reducing agents such as lithium triethoxyaluminium hydride or DBAH may also be used.

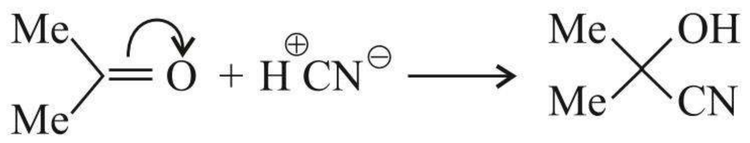
Mechanism:

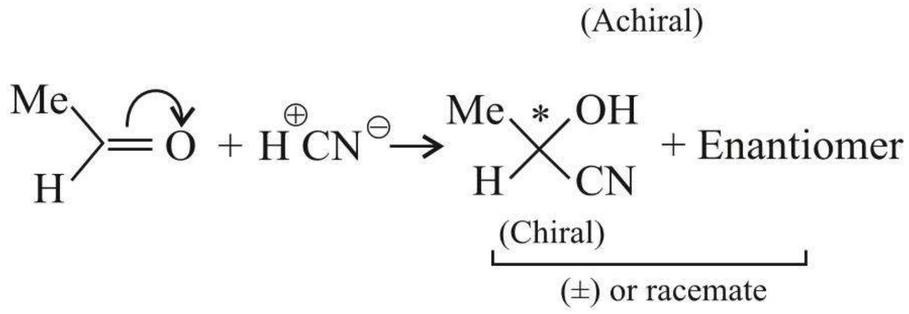


c. i. 

ii. 

It gives geometrical isomers (diastereomers) which can be separated. Similar reactions are possible with other derivatives of ammonia, i.e., NH_2NH_2, $PhNHNH_2$, 2,4-DNP, semicarbazide ($H_2NNHCONH_2$), etc. Similarly, HCHO, PhCOPh (benzophenone), $MeCH_2COCH_2Me$ (pentan-3-one), etc., will give one compound, whereas MeCHO, PhCOMe (acetophenone), PhCHO, and $MeCH_2COMe$ (butan-2-one) will give two geometrical isomers.

d. i. 

ii. 

It gives enantiomers (optical isomers) due to the chiral centre. They are difficult to separate since the chemical and physical properties of enantiomers are same. However, they can be separated by biochemical method using enzymes and making their diastereomers.

Similarly, HCHO, MeCOMe, PhCOPh (benzo-pehenone), $MeCH_2COCH_2Me$ (pentan-3-one) will give only one compound, whereas MeCHO, PhCOMe (aceto-phenone), and $MeCOCH_2Me$ (butan-2-one) will give two optical isomers.

e. 3-Pentanone undergoes NA reaction with HCN, NH_3, ROH, etc., but with $NaHSO_3$, it does not react. This is due to the following:

i. Large-sized nucleophile (SO_3^{2-}).

ii. Due to steric hindrance by two bulky ethyl group.

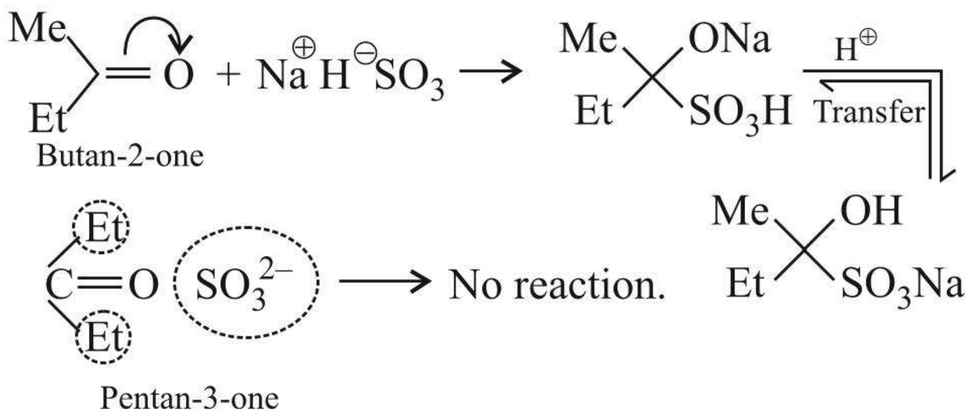
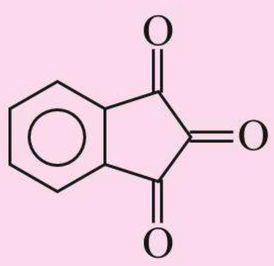


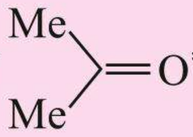
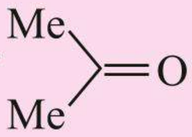
ILLUSTRATION 5.7

Explain:

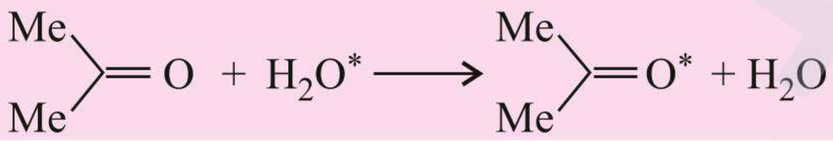
a. Chloral normally exists as chloral hydrate and is used as a hypnotic drug.

b. Ninhydrin, used as a spray reagent for the detection of amino acids, exists as hydrate. Which (C═O) is hydrated?



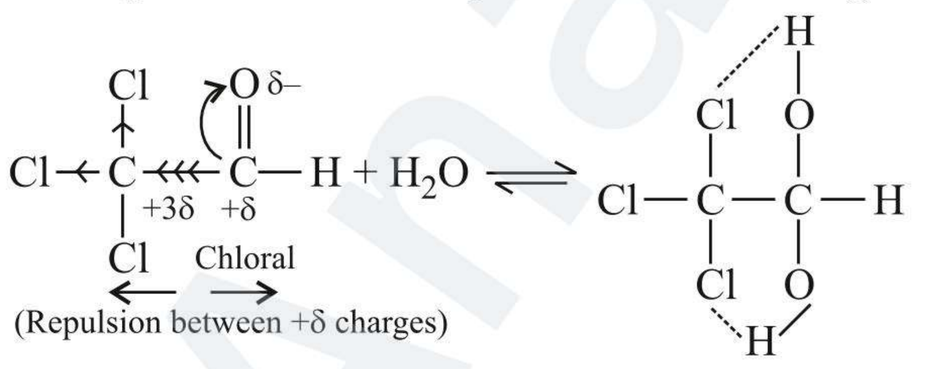
c. Account for the isolation of  from the reaction of  with H_2O^*

(O^* represents O^{18}, an isotope of O^{16}.)



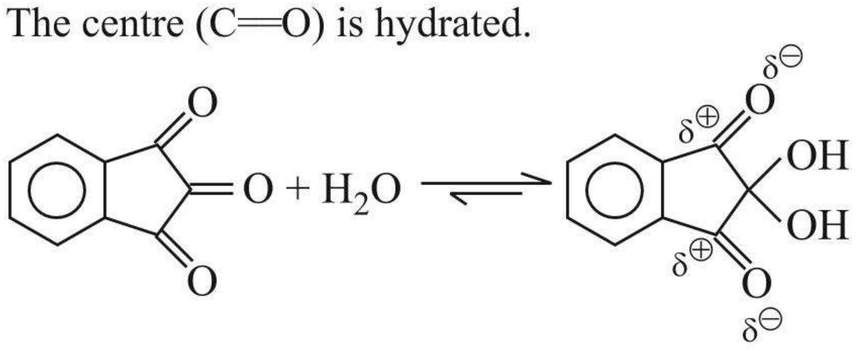
Sol.

a. In chloral, strong $\bar{e}$-withdrawing Cl atoms on C atom destabilise the carbonyl group due to repulsion between positive charges. The formation of hydrate overcomes the force of repulsion and hence equilibrium lies to the right.



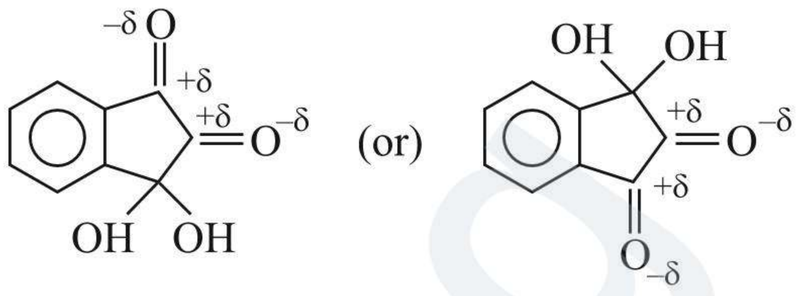
Moreover, intramolecular H-bonding is possible in chloral hydrate [between (—Cl) and (—OH) groups] which stabilises the molecule.

b. The centre (C═O) is hydrated.

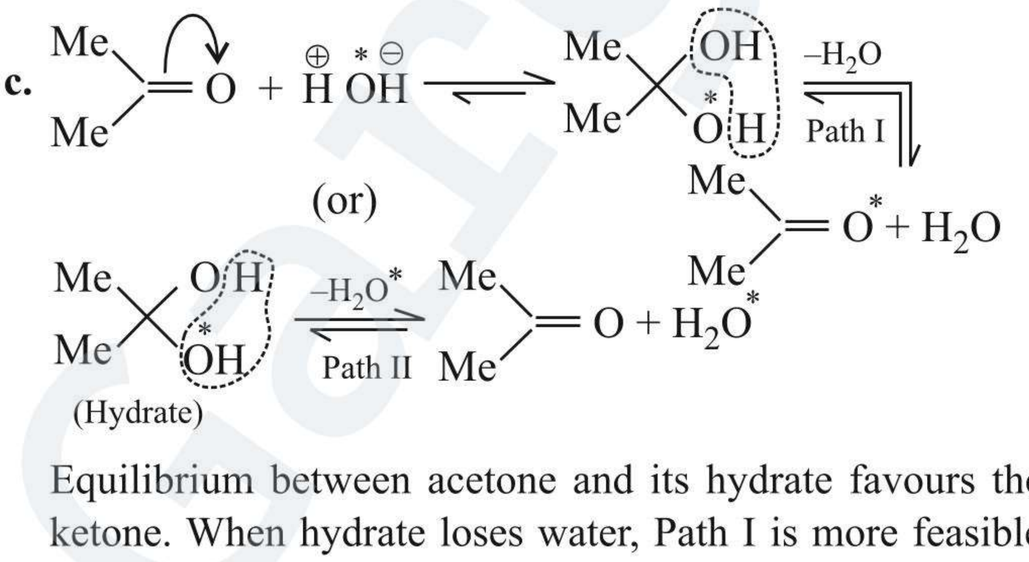


The adjacent $\delta^{\oplus}$'s are separated by the hydration of central (C═O) group.

If any terminal (C═O) is hydrated, there would be repulsion on the adjacent $+\delta$ charges, e.g.,



c.



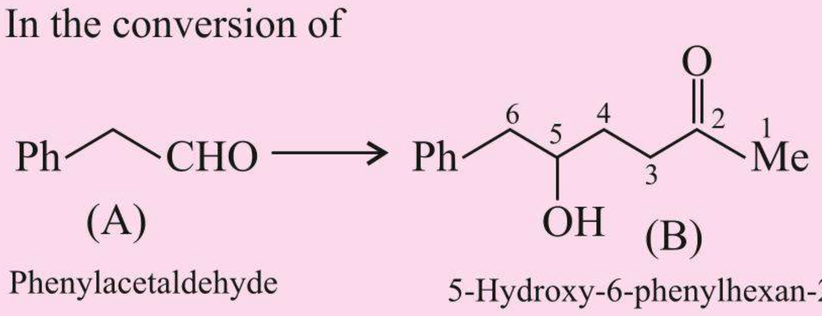
Equilibrium between acetone and its hydrate favours the ketone. When hydrate loses water, Path I is more feasible because $\left(C—\overset{*}{O}\right)$ bond is slightly stronger than (C—O) bond.

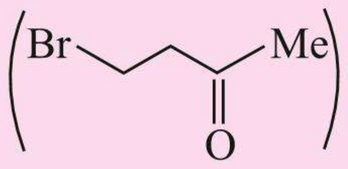
ILLUSTRATION 5.8

Explain:

a. Oximes are more acidic than hydroxylamine.

b. In the conversion of



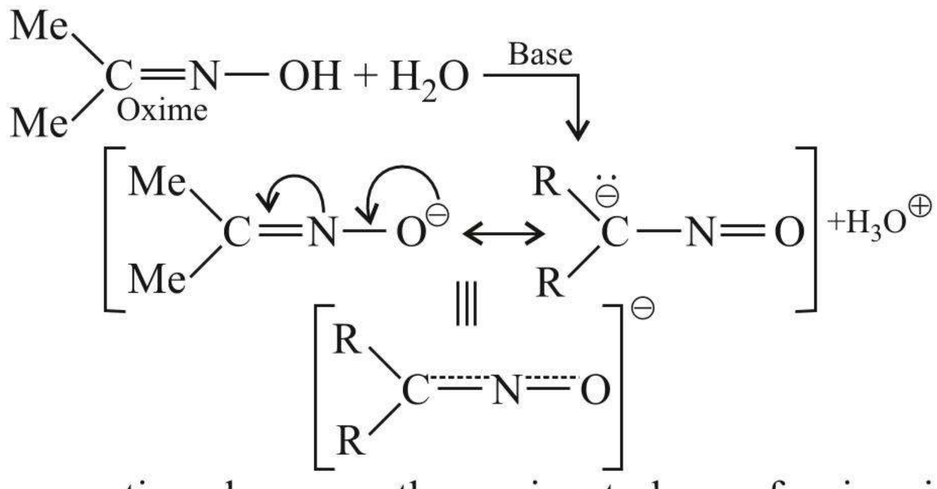
by using Grignard reagent of  (I), why (C═O) group is protected?

Sol. **a. i.** $NH_2OH + H_2O \rightleftharpoons NH_2O^{\ominus} + H_3O^{\oplus}$

Hydroxylamine

Loss of $H^{\oplus}$ from NH_2OH gives conjugate base $NH_2O^{\ominus}$ in which negative charge is localised on O atom. $NH_2O^{\ominus}$ is not stabilised; so the reaction is reversible.

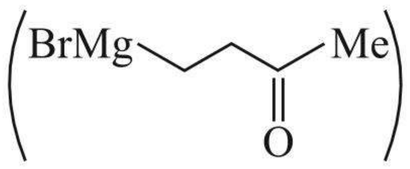
ii.

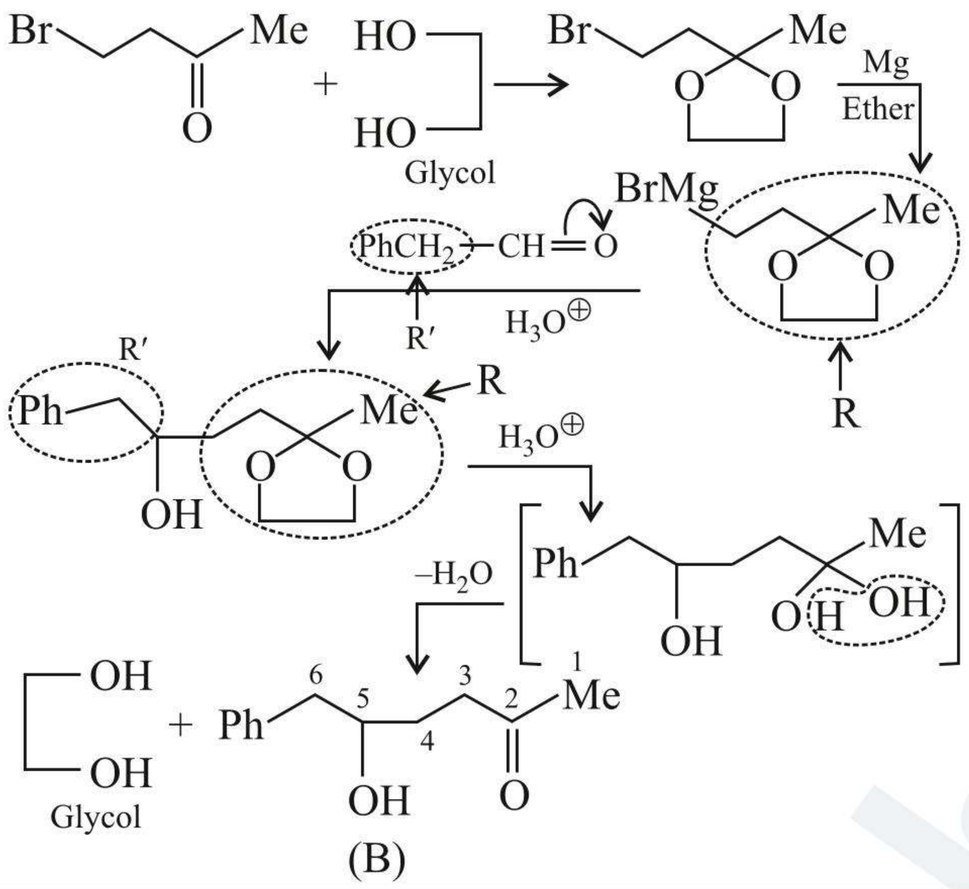


The negative charge on the conjugate base of oxime is resonance stabilised by the delocalisation of negative charge by extended π-bond, as shown above. So the reaction is

irreversible. Hence, $R_2C{=}N{-}O^{\ominus}$ is a weaker base and its conjugate acid, the oxime ($R_2C{=}N{-}OH$) is more acidic.

Thus, oximes are more acidic than hydroxylamine.

b. If (C=O) group in the compound (I) is not protected, the G.R. of (I)  will react with the (C=O) group in another molecule as it forms. So, before making G.R. of (I), (C=O) group is protected by cyclic acetal formation.



5.22 REDUCTION REACTIONS

5.22.1 Reduction of Carbonyl Compounds to Alcohol

Aldehydes and ketones are reduced to 1° and 2° alcohols, respectively, by $NaBH_4$, LAH and by catalytic hydrogenation (see Chapter 2).

5.22.2 Reduction of Carbonyl Compounds to Hydrocarbons

Reduction of (C=O) group to ($-CH_2$) group is carried out with **Clemmensen reduction** (with Zn – Hg/HCl) and with **Wolff–Kishner reduction** (with NH_2NH_2 followed by heating with NaOH or KOH in high boiling solvent, ethylene glycol) (see Chapter 2).

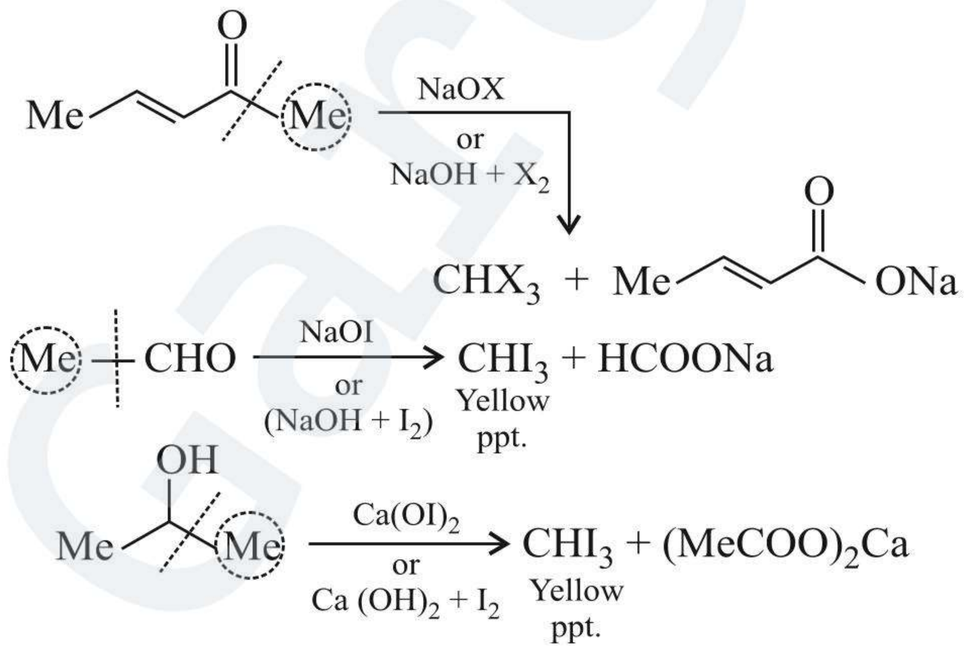
5.23 OXIDATION REACTION

Aldehydes are easily oxidised to carboxylic acid with acidic or basic $KMnO_4$, $K_2Cr_2O_7$, HNO_3, and with Tollens or Fehling's reagent.

Ketones are oxidised with strong oxidising agents at high temperature to give a mixture of carboxylic acids having lesser number of C atoms than the parent ketone. The oxidation takes place by **Popoff's rule** (see Chapter 2).

5.23.1 Oxidation of Methyl Ketone and Acetaldehyde by Haloform Reaction

Aldehydes and ketones containing at least one (Me) group linked to C atom of (C=O) group are oxidised by sodium or potassium or calcium hypohalite [NaOX, KOX, or $Ca(OX)_2$] to sodium or potassium or calcium salts of corresponding carboxylic acids having one C atom less than that of carbonyl compounds. The (Me) group is converted to haloform. This oxidation does not affect (C=C) bond, e.g.,



Alcohols containing $\left(\begin{matrix}\text{MeCH}-\\ |\\ \text{OH}\end{matrix}\right)$ group are also oxidised by iodoform or haloform reaction.

Illustration 5.9

Explain:

Propanol on oxidation with acidic $K_2Cr_2O_7$ can give propanal although in poor yield.

Sol. If the aldehyde is more volatile than the reactant alcohol and H_2O, it can be removed from the reaction mixture by fractional distillation as it is formed. Boiling point of propanal is 49°C and that of propanol is 97°C. So propanol on oxidation with acidic $K_2Cr_2O_7$ first gives propanal. As it is formed, it is removed by distillation (less boiling point, 49°C) before it is converted to propanoic acid.

5.24 HALOGENATION

a. Aldehydes and ketones containing α-H atom undergo halogenation when treated with halogens in the presence of an acid or a base. However, in the presence of a base, polyhalogenation occurs (e.g., haloform reaction), but in the presence of acids, the reaction can be stopped at the monohalogenation stage by using 1 mol of the halogen.

i. $CH_3CHO + Cl_2 \xrightarrow{CH_3COOH} \underset{\alpha\text{-Chloro acetaldehyde}}{ClCH_2CHO} + HCl$

ii. $CH_3COCH_3 + Br_2 \xrightarrow{CH_3COOH} \underset{\alpha\text{-Bromoacetone}}{BrCH_2COCH_3} + HBr$

With excess of halogen, di- and tri-halogen derivatives are formed. Formaldehyde does not undergo this reaction, since it does not have α-H atom.

b. Nuclear halogenation is difficult to carry out both in aromatic aldehydes and ketones since side-chain halogenation occurs faster, e.g.,

i.

$$PhCHO + Cl_2\,(cold) \xrightarrow{\text{Low temp.}} \underset{\text{Benzoyl chloride}}{PhCOCl} + HCl$$

ii.

$$PhCOCH_3 + Br_2 \xrightarrow[AlCl_3]{Br_2,\ 273\ K} \underset{\substack{\text{Phenacyl bromide}\\ \text{(bromoacetophenone)}}}{PhCOCH_2Br} + HBr$$

(Catalytic amount)

Note: However, phenacyl chloride, a lachrymator (weeping gas), used to disperse the mob by policemen, is prepared by Friedel–Crafts reaction).

$$C_6H_6 + CH_3COCl \xrightarrow{AlCl_3} PhCOCH_3$$

$$\xrightarrow{Cl_2} PHCOCH_2Cl$$

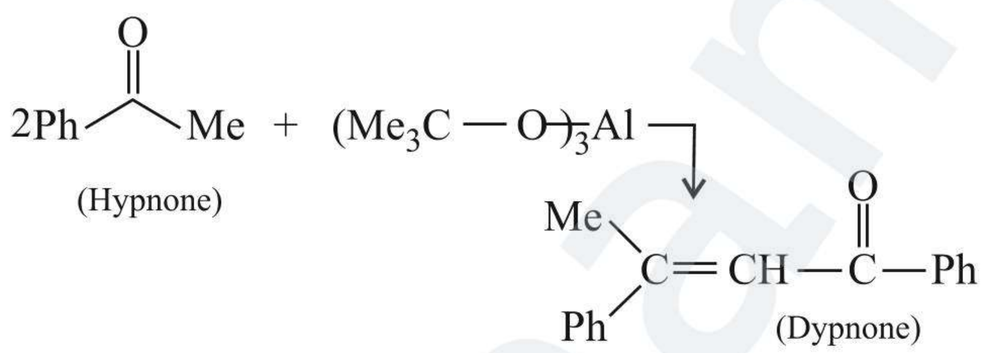
c. However, when acetophenone is treated with Br_2 in the presence of excess of anhydrous $AlCl_3$, *m*-bromo-acetophenone is formed.

$$PhCOCH_3 + Br_2 \xrightarrow[\text{excess}]{AlCl_3} m\text{-}Br{-}C_6H_4COCH_3 + HBr$$

d. Since halogens oxidise benzaldehyde to benzoic acid, therefore, halogen derivatives of benzaldehyde are prepared by indirect methods.

5.25 REACTION OF ACETOPHENONE (HYPNONE) WITH ALUMINIUM t-BUTOXIDE TO GIVE DYPNONE

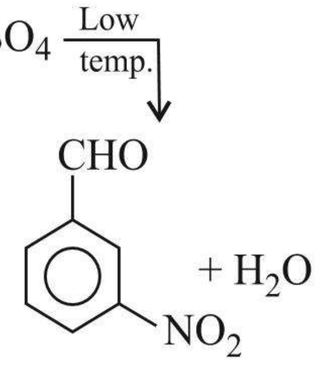
Hypnone is used as hypnotic.



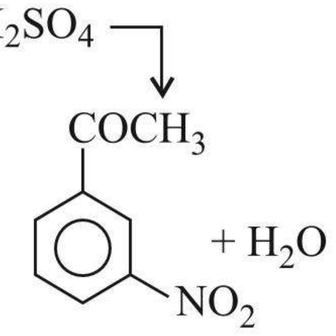
5.26 NITRATION AND SULPHONATION

Nitration of benzaldehyde gives a low yield (50%) of *m*-nitro benzaldehyde, since a part of benzaldehyde is oxidised to benzoic acid by HNO_3.

a. $PhCHO + \text{Conc. } HNO_3 + \text{Conc. } H_2SO_4 \xrightarrow[\text{temp.}]{\text{Low}}$

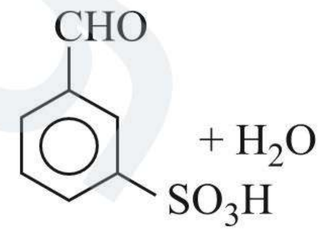


b. $PhCOCH_3 + \text{Conc. } HNO_3 + \text{Conc. } H_2SO_4 \longrightarrow$



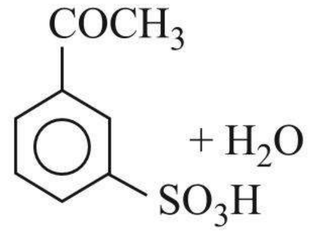
m-Nitroacetophenone

c. $PhCHO + \text{Conc. } H_2SO_4 \longrightarrow$



m-Benzaldehyde sulphonic acid
or *m*-Formyl benzene sulphonic acid

d. $PhCOCH_3 + \text{Conc. } H_2SO_4 \longrightarrow$



m-Acetophenone sulphonic acid
or *m*-Acetyl benzene sulphonic acid

5.27 POLYMERISATION

5.27.1 Formaldehyde Polymerises Readily Giving Different Products Under Different Conditions

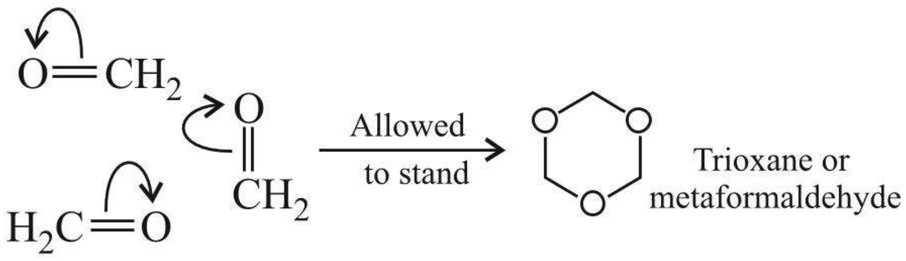
i. When an aqueous solution (40%) of HCHO, i.e., formalin is evaporated to dryness, it gives a white solid called paraformaldehyde, $(CH_2O)_n\,H_2O$, where n = 6–50.

$$n\text{-}HCHO\ (\text{Aq. soln.}) \xrightarrow{373\ K} -(CH_2-O-CH_2-O-CH_2O)-_n$$

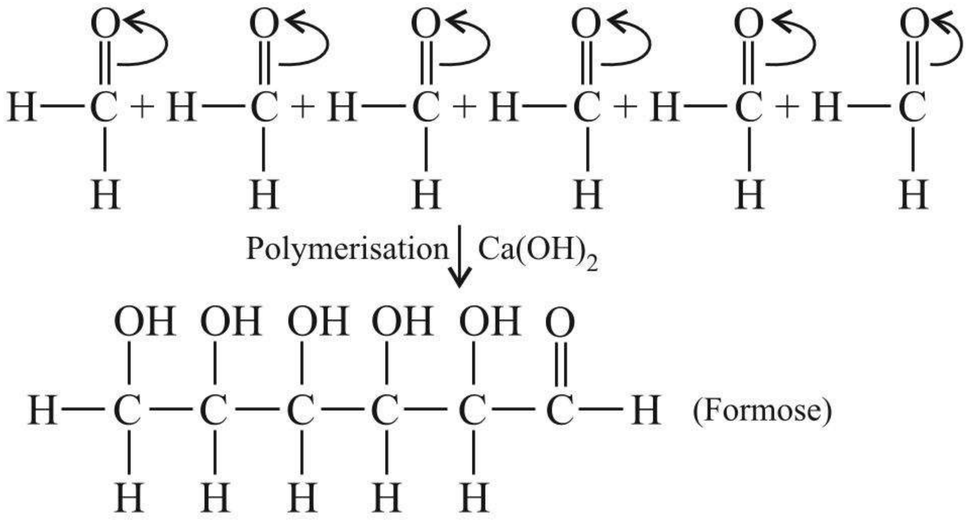
$$\underset{(CH_2O)_nH_2O}{\overset{\oplus}{C}H_2-\overset{\ominus}{O}} \cdots \underset{\text{or}}{\overset{\oplus}{C}H_2-\overset{\ominus}{O}} \cdots \underset{\text{(Paraformaldehyde)}}{\overset{\oplus}{C}H_2-\overset{\ominus}{O}}$$

ii. When an aqueous solution of HCHO (60%) is treated with a few drops of conc. H_2SO_4, it gives polyoxymethylene, $(CH_2O)_nH_2O$, where $n > 100$. It is water insoluble solid and gives back HCHO on heating.

iii. When gaseous HCHO is allowed to stand, it gives trioxane or metaformaldehyde.

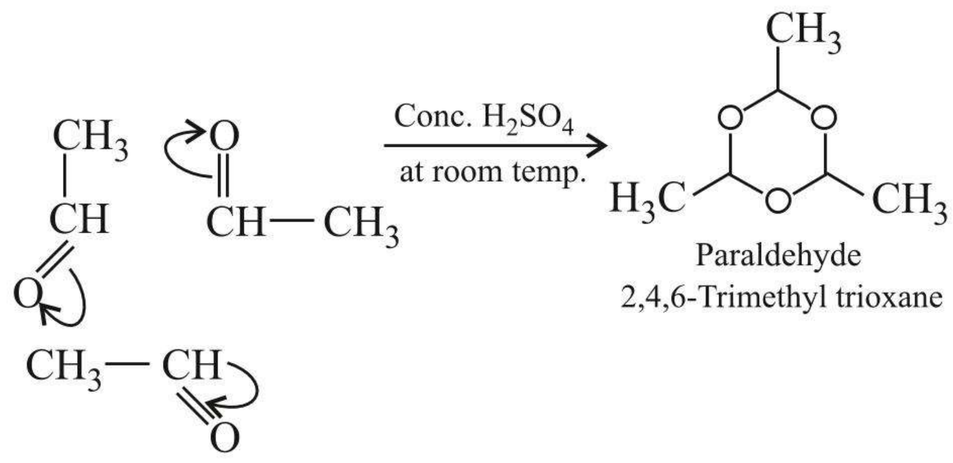


iv. When treated with a solution of $Ca(OH)_2$, six molecules of HCHO combine together to give formose which is a sugar ($C_6H_{12}O_6$).

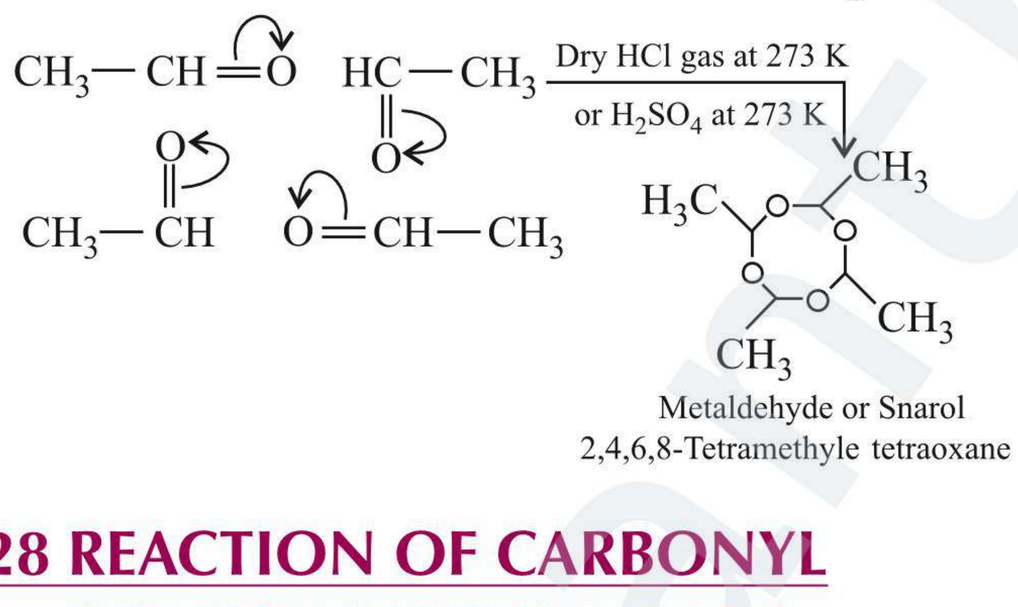


5.27.2 Polymerisation of Acetaldehyde

i. When a few drops of conc. H_2SO_4 are added to acetaldehyde at room temprature, a rapid exothermic reaction occurs and a cyclic trimer called paraldehyde is formed. It is used as a hypnotic medicine.

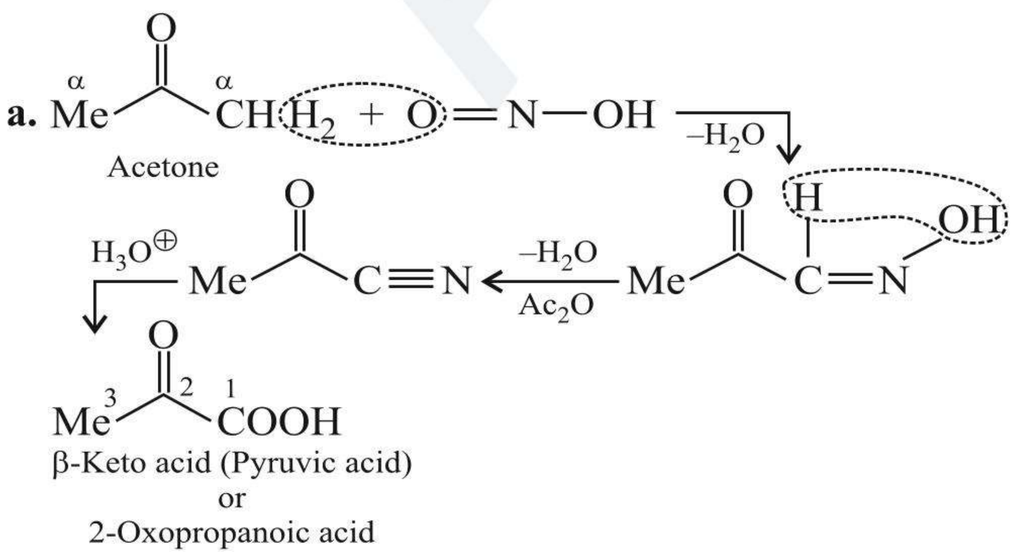


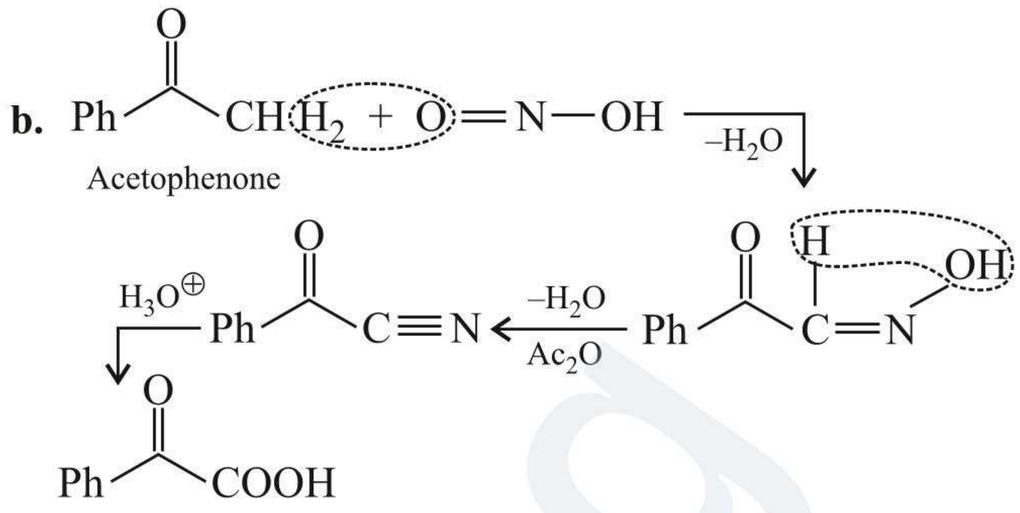
ii. When acetaldehyde is treated with dry HCl gas or a few drops of conc. H_2SO_4 at 273 K, a cyclic tetramer called metaldehyde or **Snarol** is formed. It is used to kill snails and bugs.

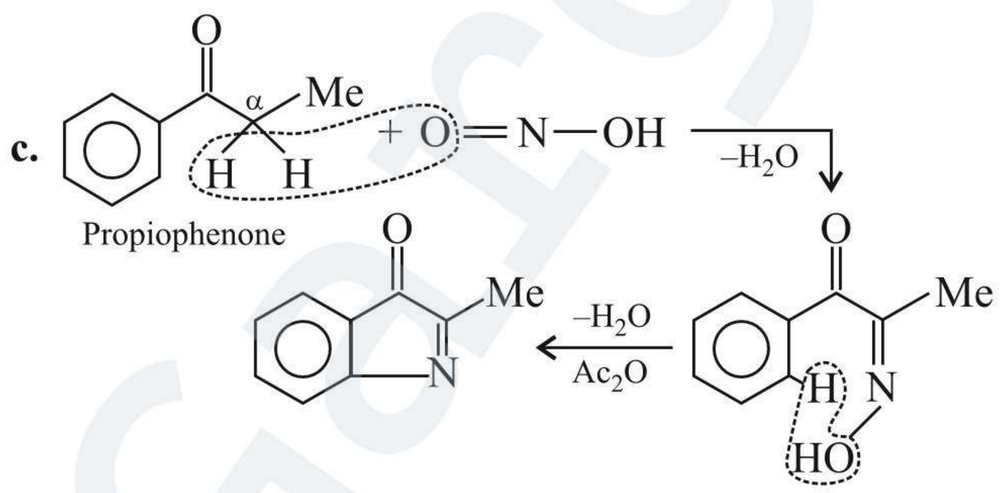


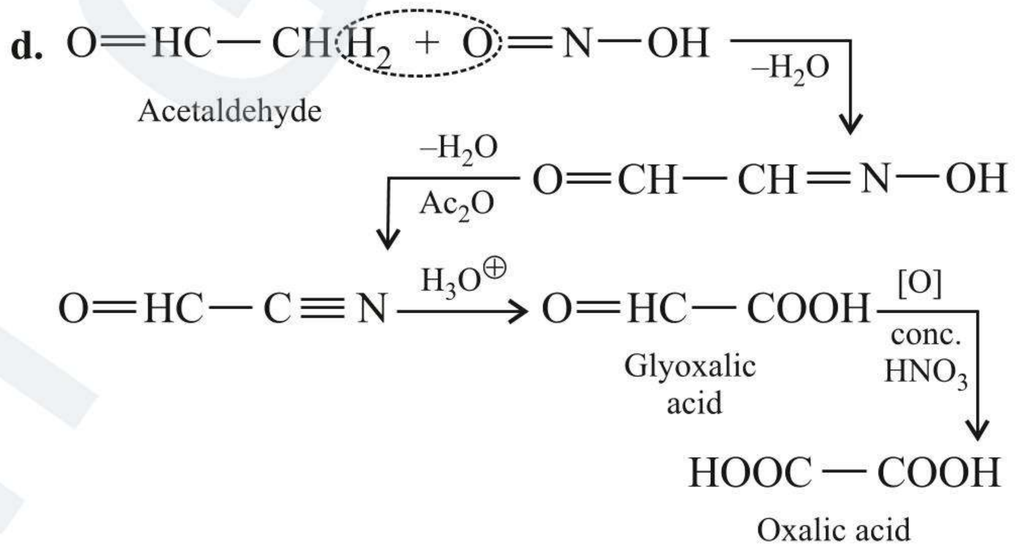
5.28 Reaction of Carbonyl Compound with HNO_2 (O=N—OH) or ($NaNO_2$ + HCl)

Carbonyl compounds react with HNO_2, produced by the reaction of ($NaNO_2$ + HCl at 0–5°C) at the α-C atom. It gives β-keto oxime which on dehydration gives keto cyanides or nitriles ($NaNO_2$ + $HCl \longrightarrow HNO_2 + NaCl$).



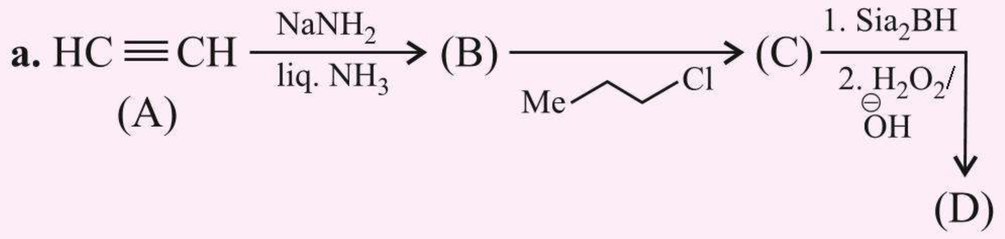


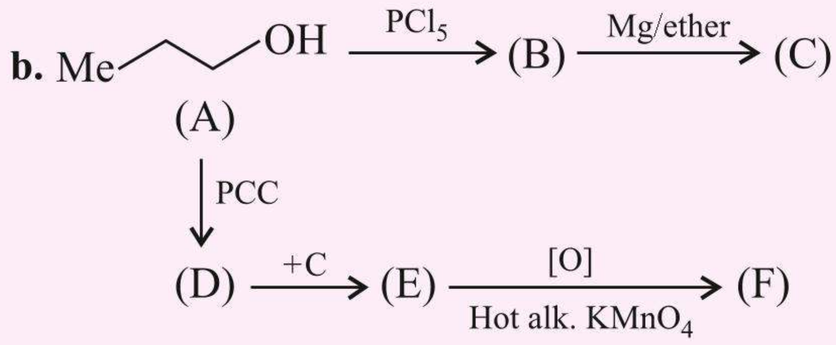


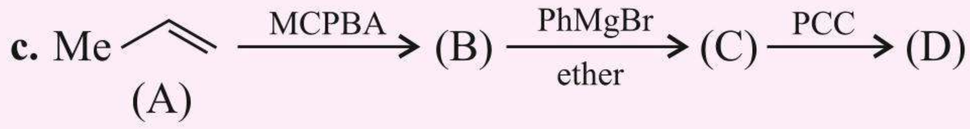


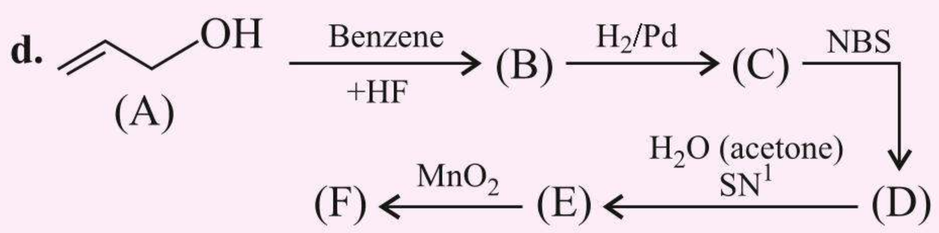
Concept Application Exercise 5.1

1. Complete the following reactions:

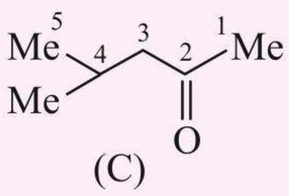








2. Complete the following reactions:

a. Alcohol (A) $\xrightarrow[(B)]{\text{Reagent}}$ 
(C)
(4-Methylpentan-2-one)

b. Alkyne (D) $\xrightarrow[(E)]{\text{Reagent}}$ Product (C)

c. Acid chloride (F) $\xrightarrow[(G)]{\text{Reagent}}$ Product (C)

d. Acid (H) $\xrightarrow[(I)]{\text{Reagent}}$ Product (C)

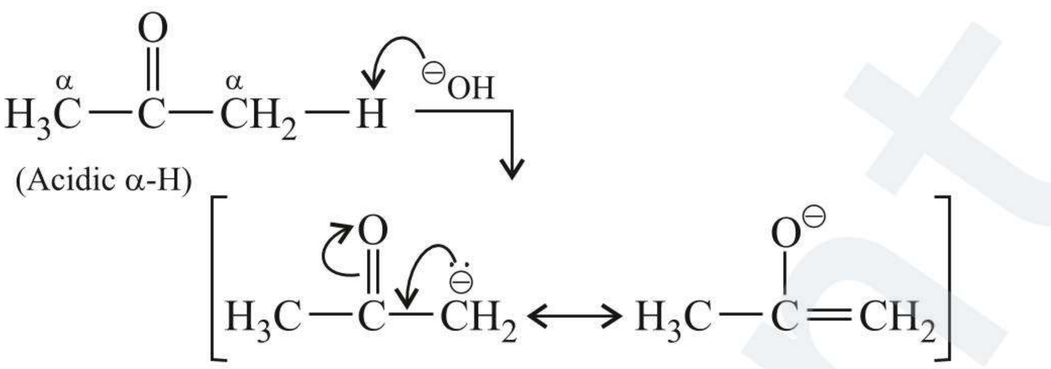
e. Nitro compound (J) $\xrightarrow[(K)]{\text{Reagent}}$ Product (C)

f. Alkyl nitrile (L) $\xrightarrow[(M)]{\text{Reagent}}$ Product (C)

5.29 ALDOL CONDENSATION

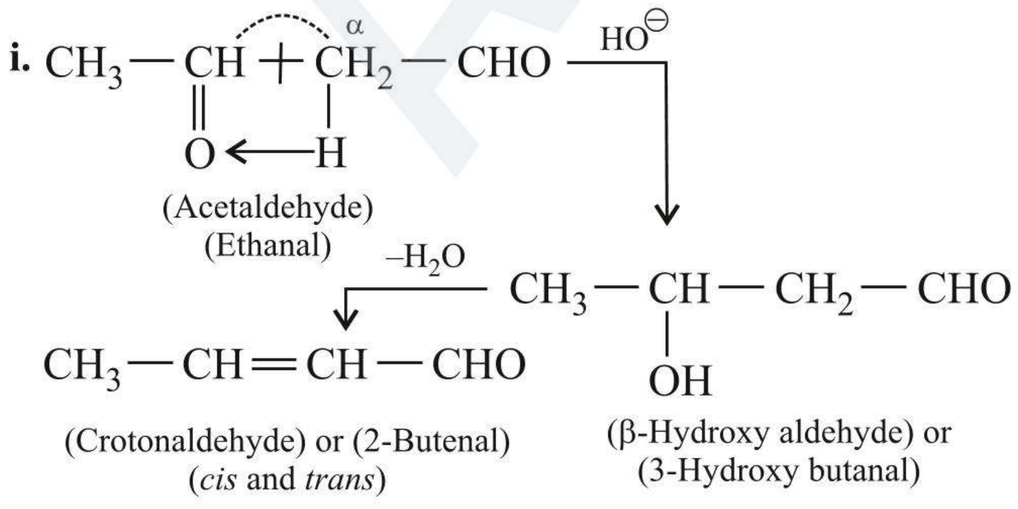
5.29.1 Reactions Due to α-H Atom

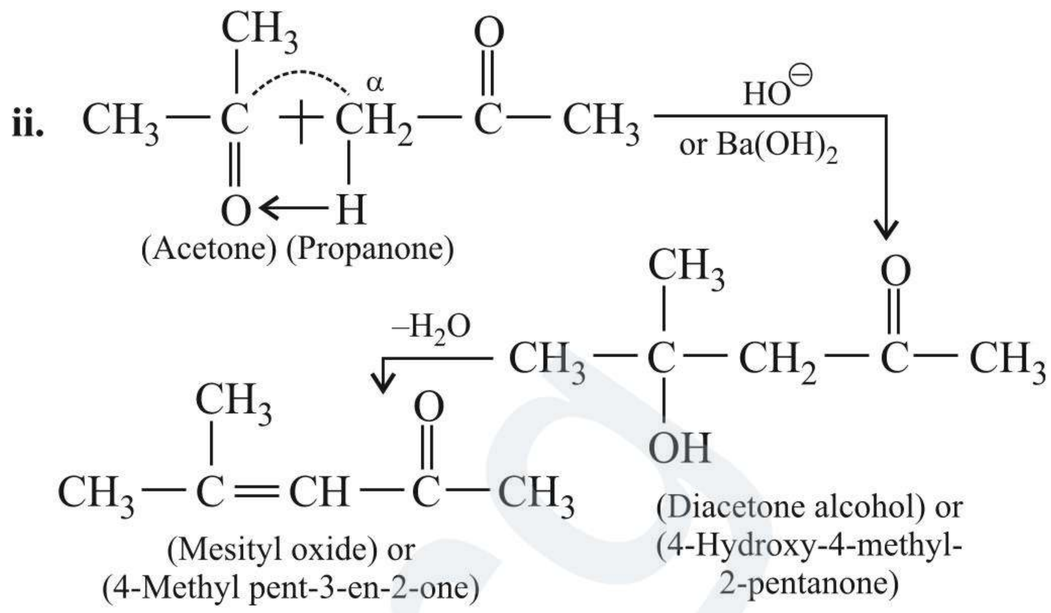
The aldehydes and ketones undergo a number of reactions due to the acidic nature of α-H, which in turn is due to the strong $\bar{e}$ -withdrawing effect of the (C═O) group and resonance stabilisation of the conjugate base.



5.29.2 Base-Catalysed Aldol Condensation

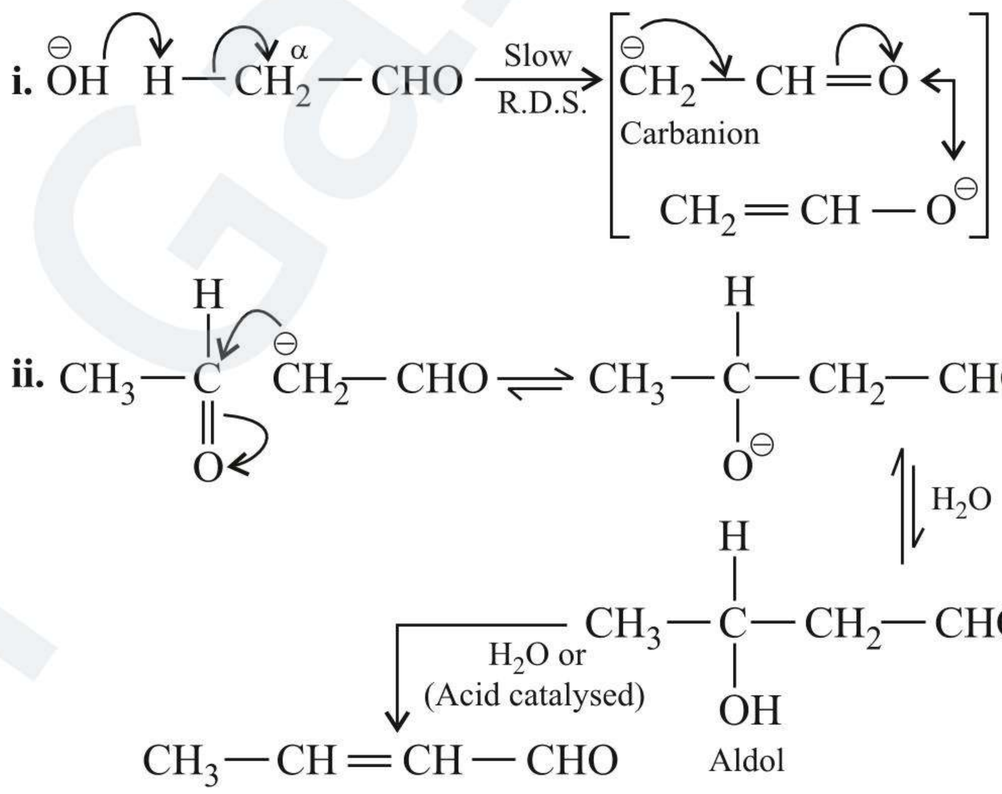
When two molecules of the same aldehyde or ketone containing α-H atom condense together in the prese-nce of dilute alkali, such as NaOH, KOH, K_2CO_3, Na_2CO_3, or at least 2 α-H-atom, to give a molecule of aldol or ketol (β-hydroxy aldehyde or ketone), it is called **aldol condensation.** On heating, it loses a molecule of H_2O to give a molecule of α,β-unsaturated aldehyde or ketone, e.g.,





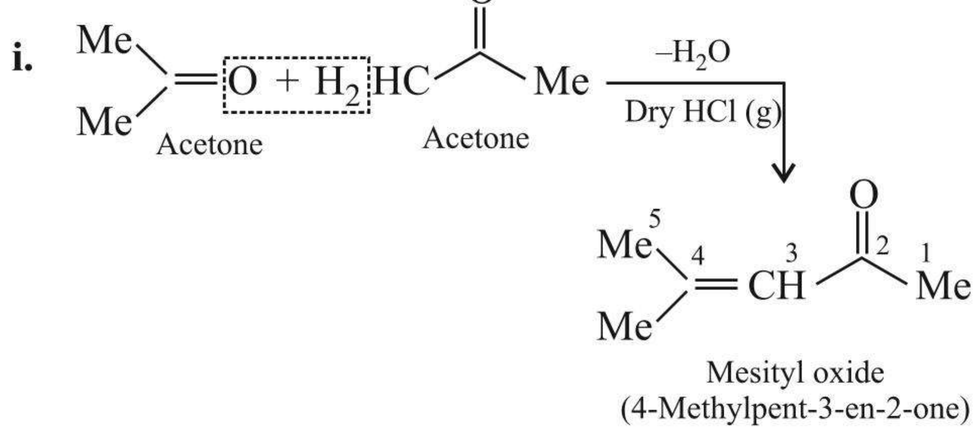
5.29.3 Mechanism

Rate = $K[\overset{\ominus}{O}H]$ [Aldehyde]; second order and bimolecular.

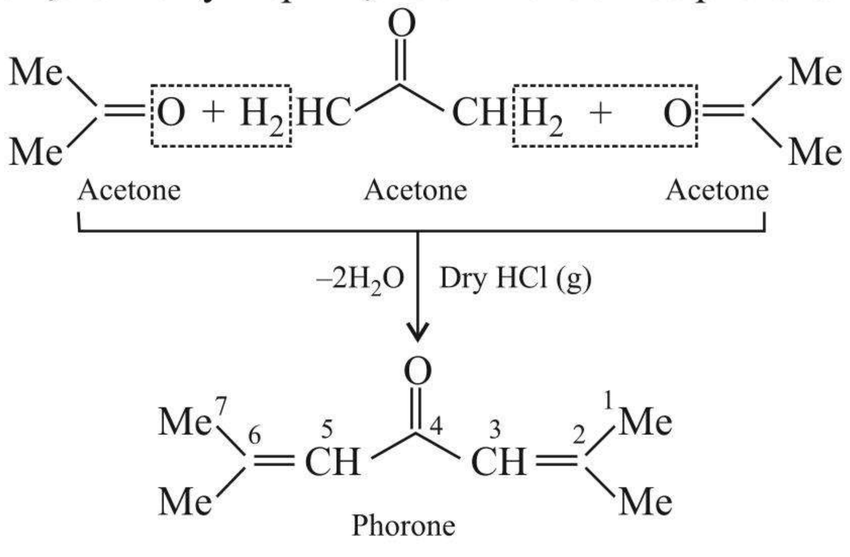


5.29.4 Acid-Catalysed Aldol Condensation

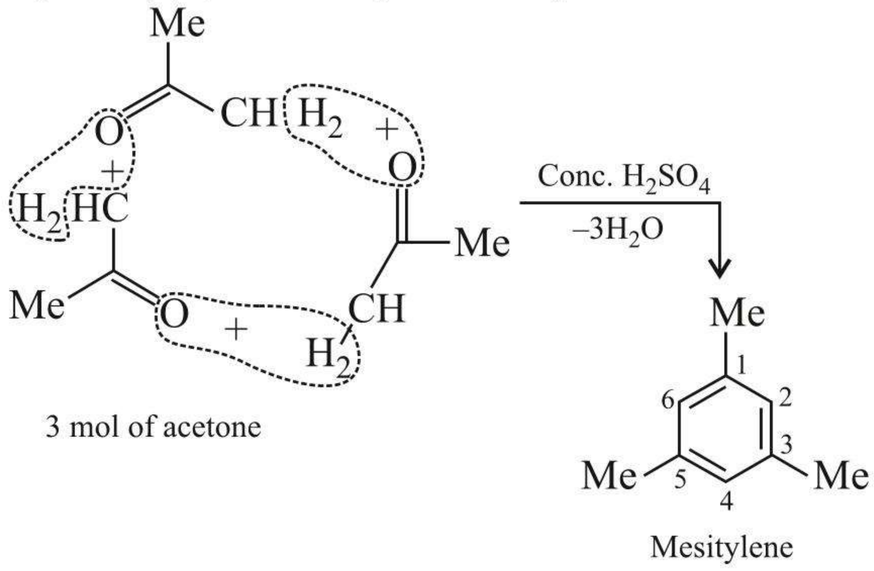
Aldol condesation can also be brought about with acid catalysis. Acetone with HCl gives mesityl oxide (4-methylpent-3-en-2-one). In general, acid-catalysed aldol reaction leads to dehydration of the initially formed aldol addition product.



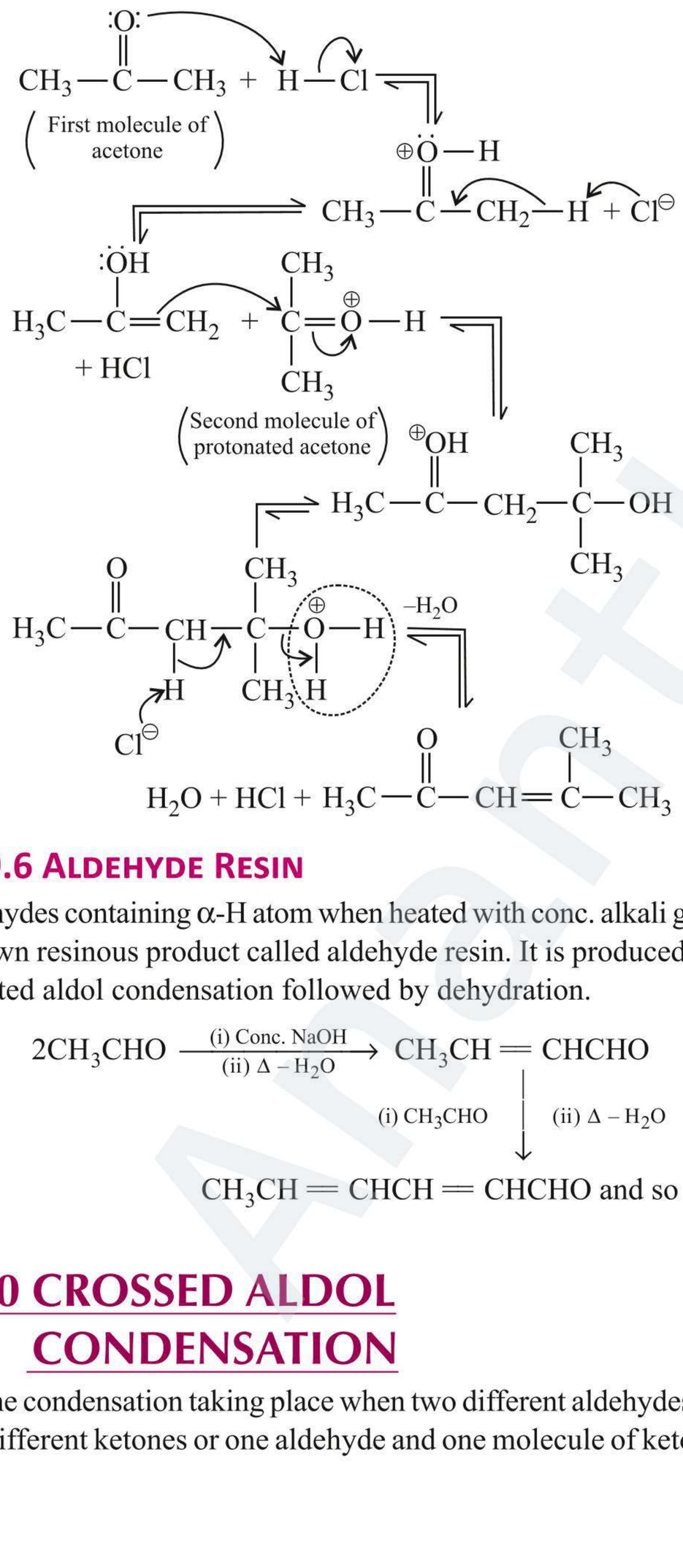
The acid-catalysed aldol condensation of acetone also produces some 2,6-dimethyl hepta-2,5-dien-4-one called phorone.



ii. Heating acetone with H_2SO_4 leads to the formation of mesitylene (1,3,5-trimethyl benzene).



5.29.5 Mechanism



5.29.6 Aldehyde Resin

Aldehydes containing α-H atom when heated with conc. alkali give a brown resinous product called aldehyde resin. It is produced by repeated aldol condensation followed by dehydration.

$$2CH_3CHO \xrightarrow[(ii)\ \Delta - H_2O]{(i)\ \text{Conc. NaOH}} CH_3CH=CHCHO$$

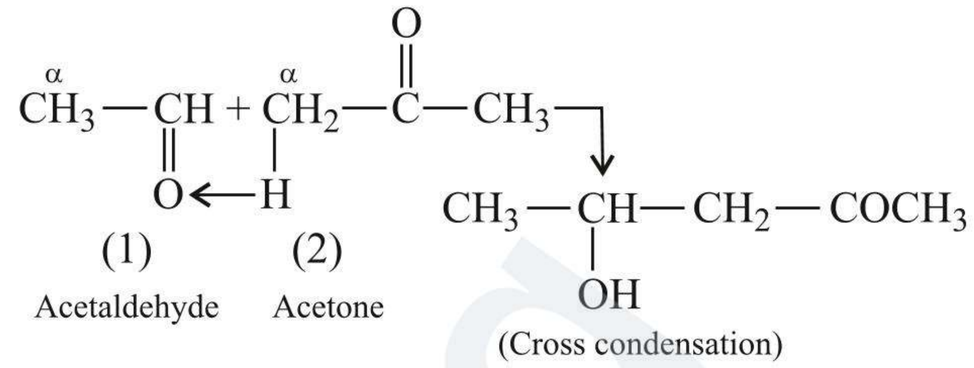
$$CH_3CH=CHCH=CHCHO \text{ and so on}$$

(i) CH_3CHO (ii) $\Delta - H_2O$

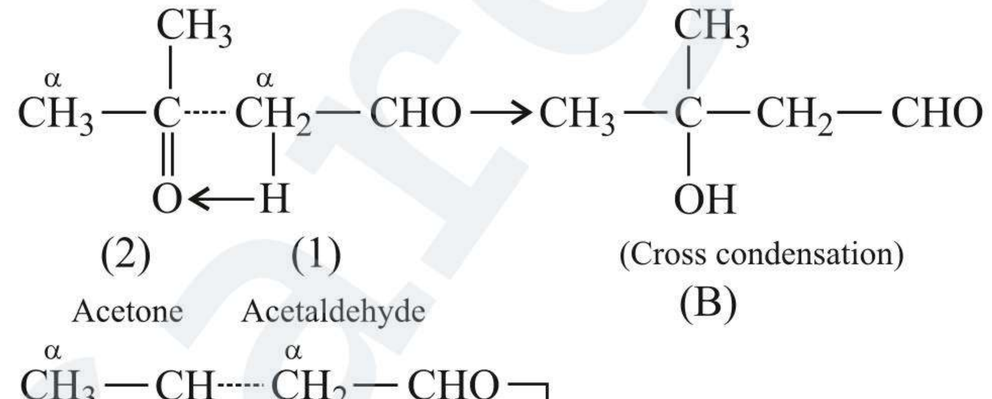
5.30 Crossed Aldol Condensation

It is the condensation taking place when two different aldehydes or two different ketones or one aldehyde and one molecule of ketone both containing α-H atoms. A number of products due to self-condensation and cross condensation are obtained, for example,

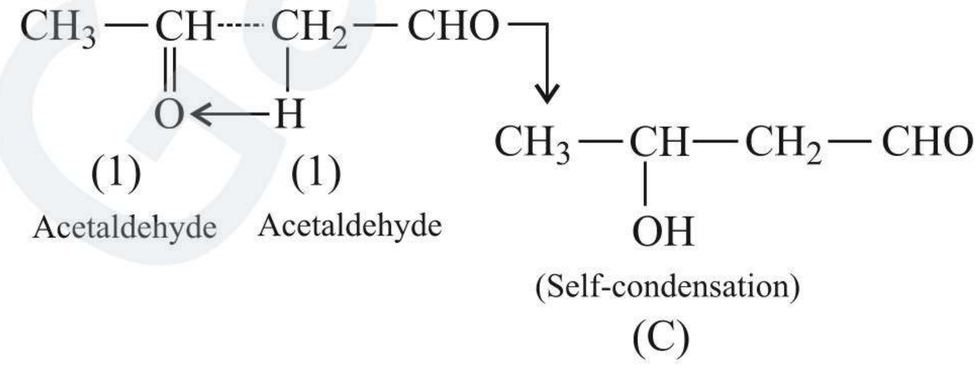
i.



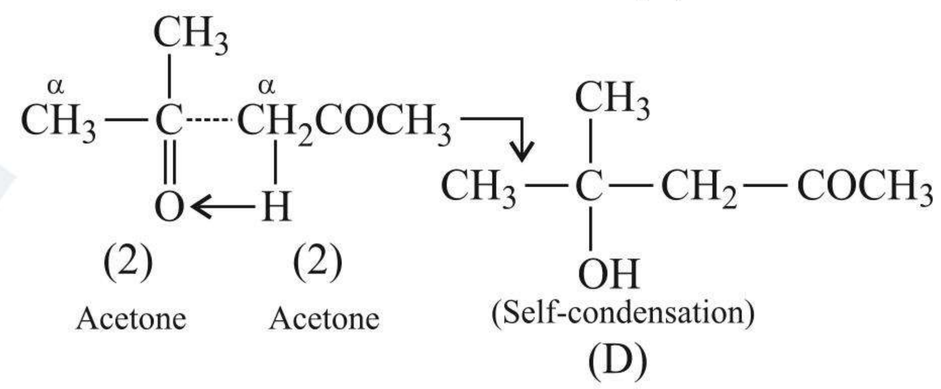
ii.



iii.



iv.



The ease and percentage of formation: A > C > B > D (since reactivity of aldehydes is more than that of ketones).

In (A), ketones are better carbanion sources and aldehydes are good acceptors. In other words, ketone carbanions are better nucleophiles than aldehyde carbanions.

Acidic character: $CH_3CHO > CH_3COCH_3$

Basic and nucleophilic characters:

$^{\ominus}CH_2CHO < {}^{\ominus}CH_2COCH_3$

So the formation of (A) is easier and is in major amount.

In (C), both carbanion source and acceptor are aldehydes.

In (B), aldehyde is carbanion and ketone is acceptor.

In (D), both carbanion source and acceptor are ketones.

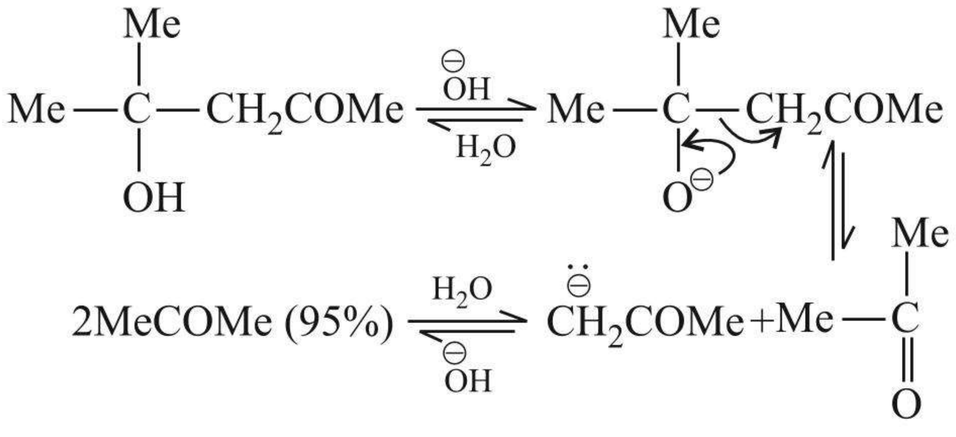
So the ease of formation and percentage of formation is A > C > B > D.

Table 5.4 Number of products formed during crossed aldol condensation

S.No.	Carbonyl compound (1)	Carbonyl compound (2)	Self-condensation products	Cross-condensation products	Total products
1.	Containing one type of similar α-H atoms or symmetrical ketones For example:	Containing one type of similar α-H atoms or symmetrical ketones	One product from (a) and one from (b)		
	a. $CH_3\overset{\alpha}{}-CHO$ with	b. $CH_3\overset{\alpha}{C}H_2CHO$	2	2	4
	a. $CH_3\overset{\alpha}{}-CHO$ with	b. $CH_3\overset{\alpha}{C}O\overset{\alpha}{C}H_3$	2	2	4
	a. $CH_3\overset{\alpha}{C}H_2CO\overset{\alpha}{C}H_2CH_3$ (Pentan-3-one) with	b. $CH_3\overset{\alpha}{C}H_2CHO$ or $\overset{\alpha}{C}H_3CO\overset{\alpha}{C}H_3$	2	2	4
2.	Containing two different types of dissimilar α-H atoms or unsymmetrical ketones For example:	Containing one type of similar α-H atoms or symmetrical ketones	Two products from (a) and two from (b)		
	a. $CH_3\overset{\alpha'}{C}O\overset{\alpha}{C}H_2CH_3$ (Butan-2-one) with	b. $CH_3\overset{\alpha}{C}H_2CHO$ or $\overset{\alpha}{C}H_3CO\overset{\alpha}{C}H_3$ or $CH_3\overset{\alpha}{C}H_2CHO$ or $\overset{\alpha}{C}H_3CHO$	3	3	6
3.	Containing two different types of dissimilar α-H atoms or unsymmetrical ketone For example:	Containing two different types of dissimilar α-H atoms or unsymmetrical ketones	Two products from (a) and two from (b)		
	a. $CH_3\overset{\alpha'}{C}O\overset{\alpha}{C}H_2CH_3$ with	b. $Ph\overset{\alpha'}{C}H_2CO\overset{\alpha}{C}H_2CH_3$	4	4	8
Maximum number of cross- and self-aldol products = 8					

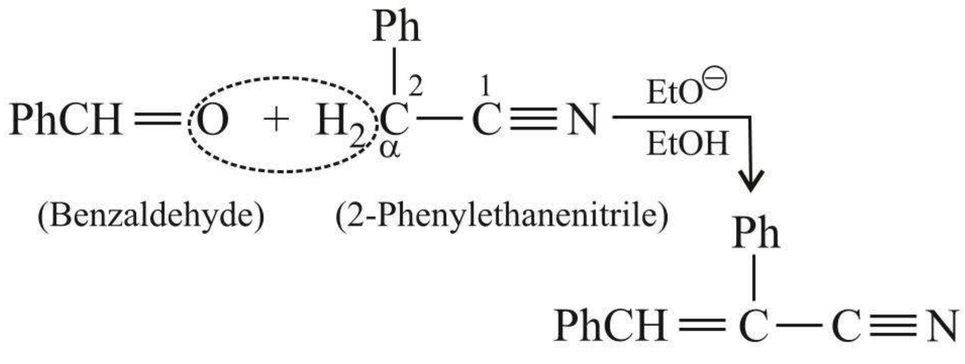
5.31 REVERSIBILITY OF ALDOL ADDITIONS

The aldol addition is reversible. When aldol addition product obtained from acetone is heated with strong base, it reverts to an equilibrium mixture that consists largely (~ 95%) of acetone. It is called **retro-aldol reaction.**



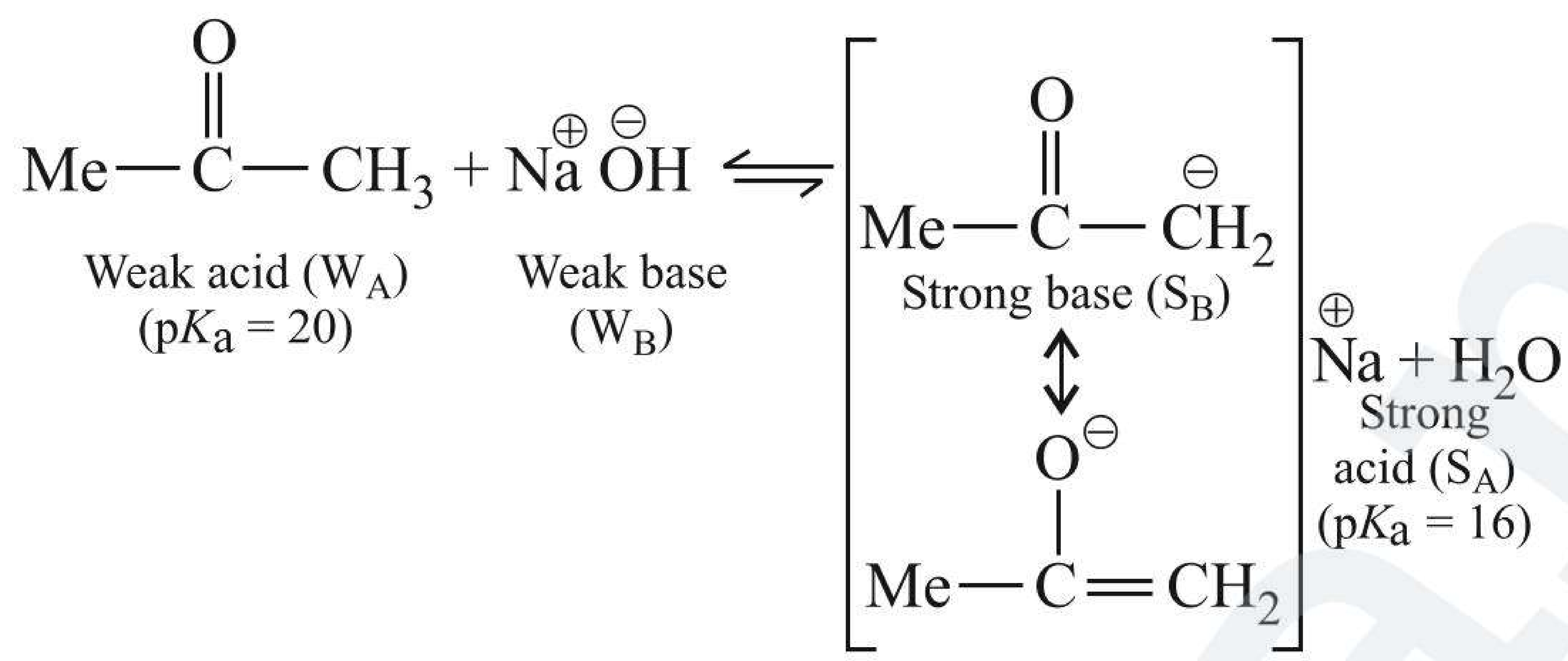
5.32 CONDENSATION WITH NITRILES

The α-H atoms of nitriles are also acidic; but less than those of carbonyl compounds (e.g., pK_a of $CH_3CN = 25$). Therefore, nitriles having α-H atom with comparable acidities undergo condensation of the aldol type, for example,



5.33 CONDENSATION WITH LDA (LITHIUM DIISOPROPYL AMIDE, $((i\text{-Pr})_2\overset{\ominus}{N}\overset{\oplus}{Li})$ THF

Formation of enolate anion depends on the strength of the base used. If a weaker base than the enolate anion is used, then the equilibrium lies to the left, e.g.,

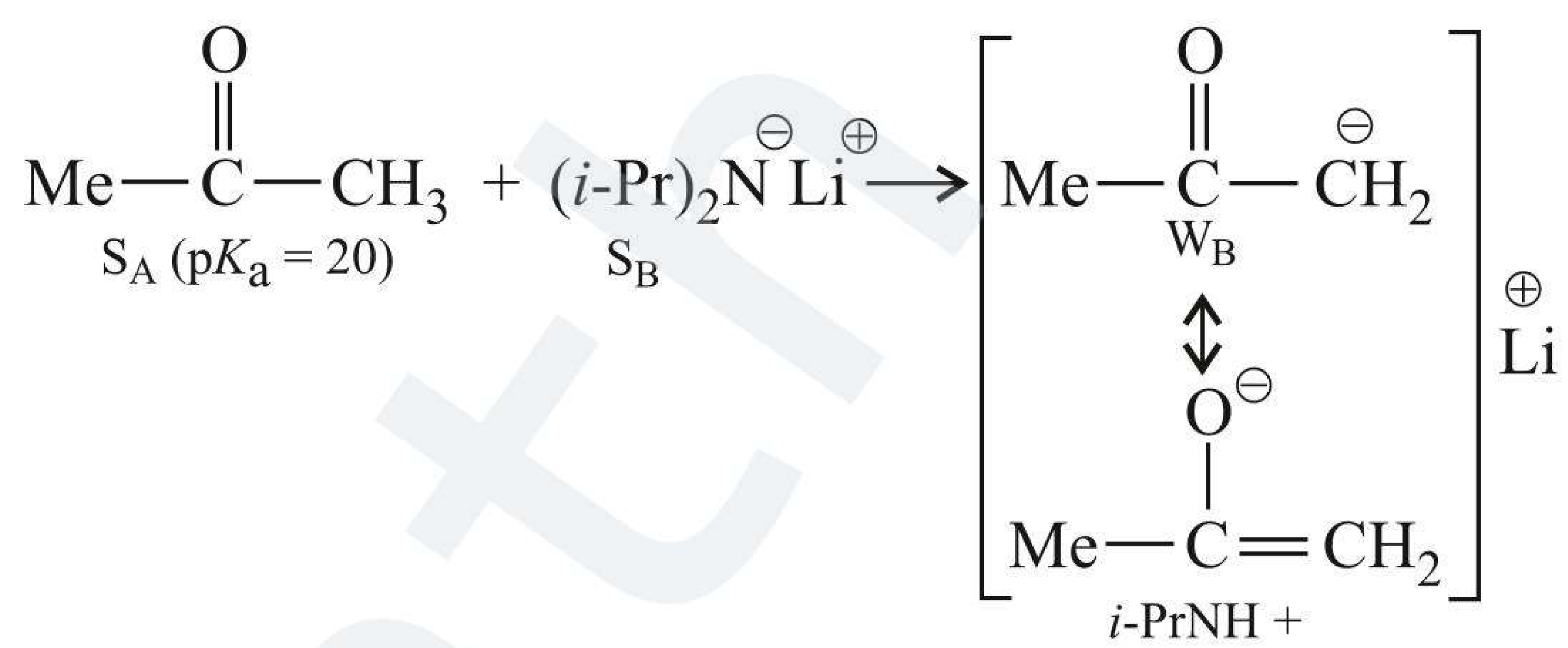


Equilibrium lies to the W_A and W_B side.

If a strong bulky base, like LDA (lithium diisopropyl amide,

$$\left[\left(\begin{matrix}Me\\Me\end{matrix}\!\!>\right)_2\overset{\ominus}{N}\overset{\oplus}{Li} \text{ or } (Me_2CH)_2\overset{\ominus}{N}\overset{\oplus}{Li} \text{ or } (i\text{-}C_3H_7)_2\overset{\ominus}{N}\overset{\oplus}{Li} \text{ or } (i\text{-Pr})_2\overset{\ominus}{N}\overset{\oplus}{Li}\right]$$

is used, the equilibrium lies to the right.

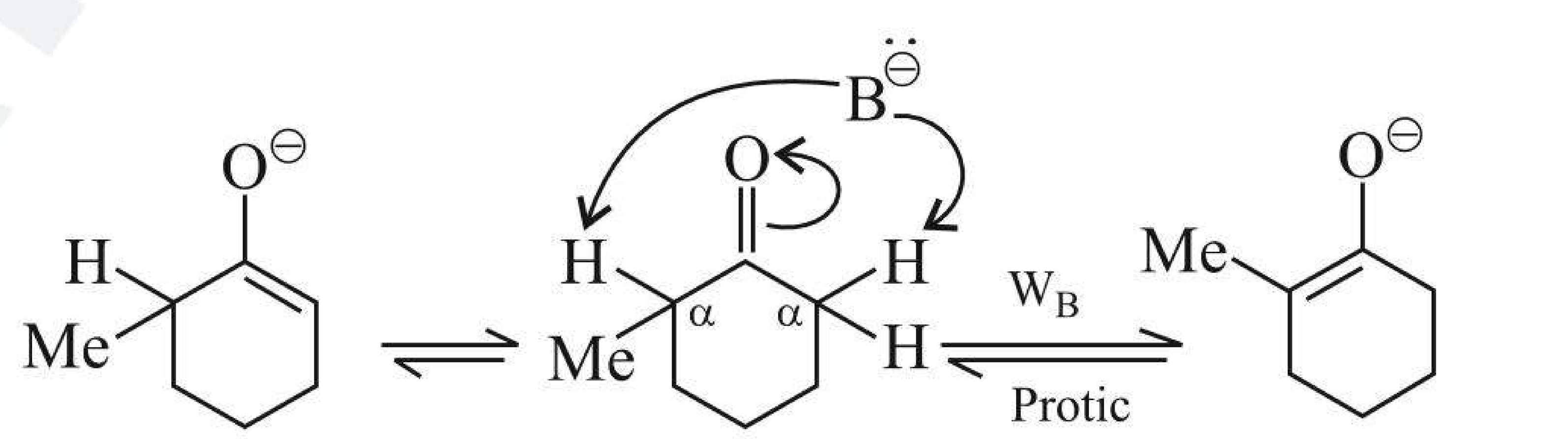


LDA is prepared by reacting diisopropyl amine $(i\text{-Pr})_2NH$ with RLi (alkyl lithium) in THF or diethyl ether solvent.

$$\underset{S_A\ (pK_a = 38)}{(i\text{-Pr})_2NH} + \underset{\text{Butyl lithium } (S_B)}{\overset{-\delta}{C_4H_9}\ \overset{+\delta}{Li}} \xrightarrow{THF} \underset{W_B}{(i\text{-Pr})_2N}\overset{\oplus}{Li} + \underset{W_A\ (pK_a = 50)}{C_4H_{10}}$$

5.33.1 Regioselective Formation of Enolate Anion

2-Methyl cyclohexanone, an unsymmetrical ketone, can form two enolates. With a weak base in protic solvent, it forms a thermodynamically more stable enolate having more substituted double bond, e.g.,



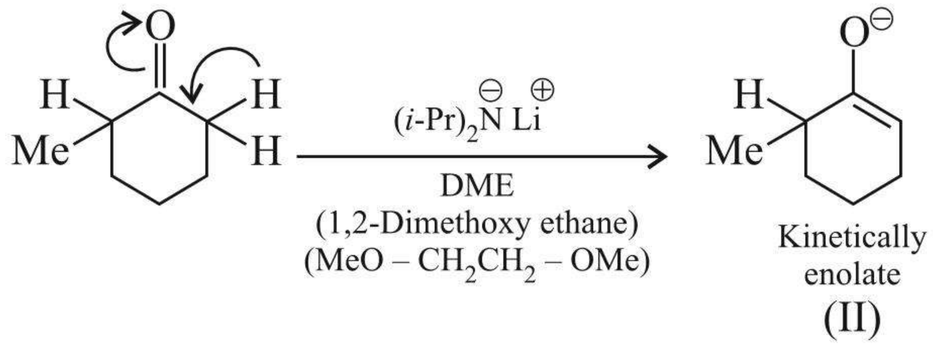
Kinetically less stable enolate (Less substituted double bond) (II)

2-Methylcyclo hexanone (A)

Thermodynamically more stable enolate (More substituted double bond) (I)

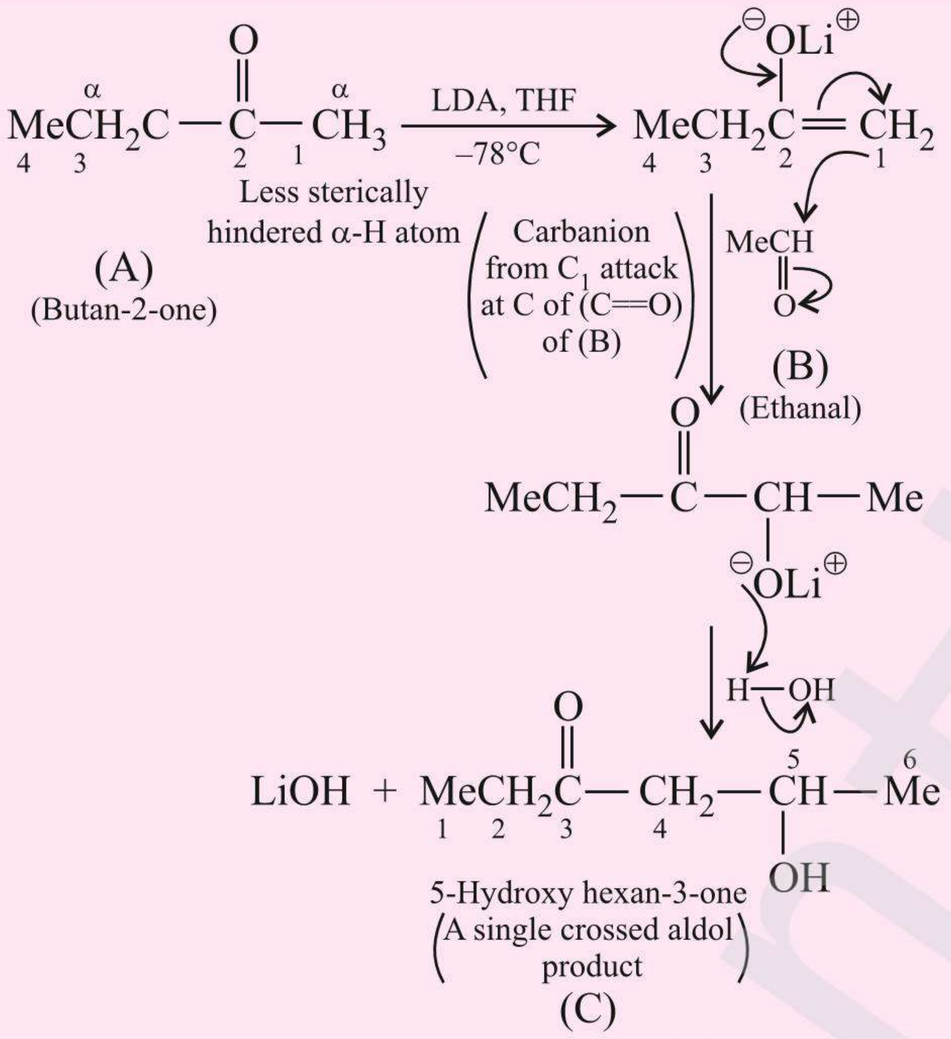
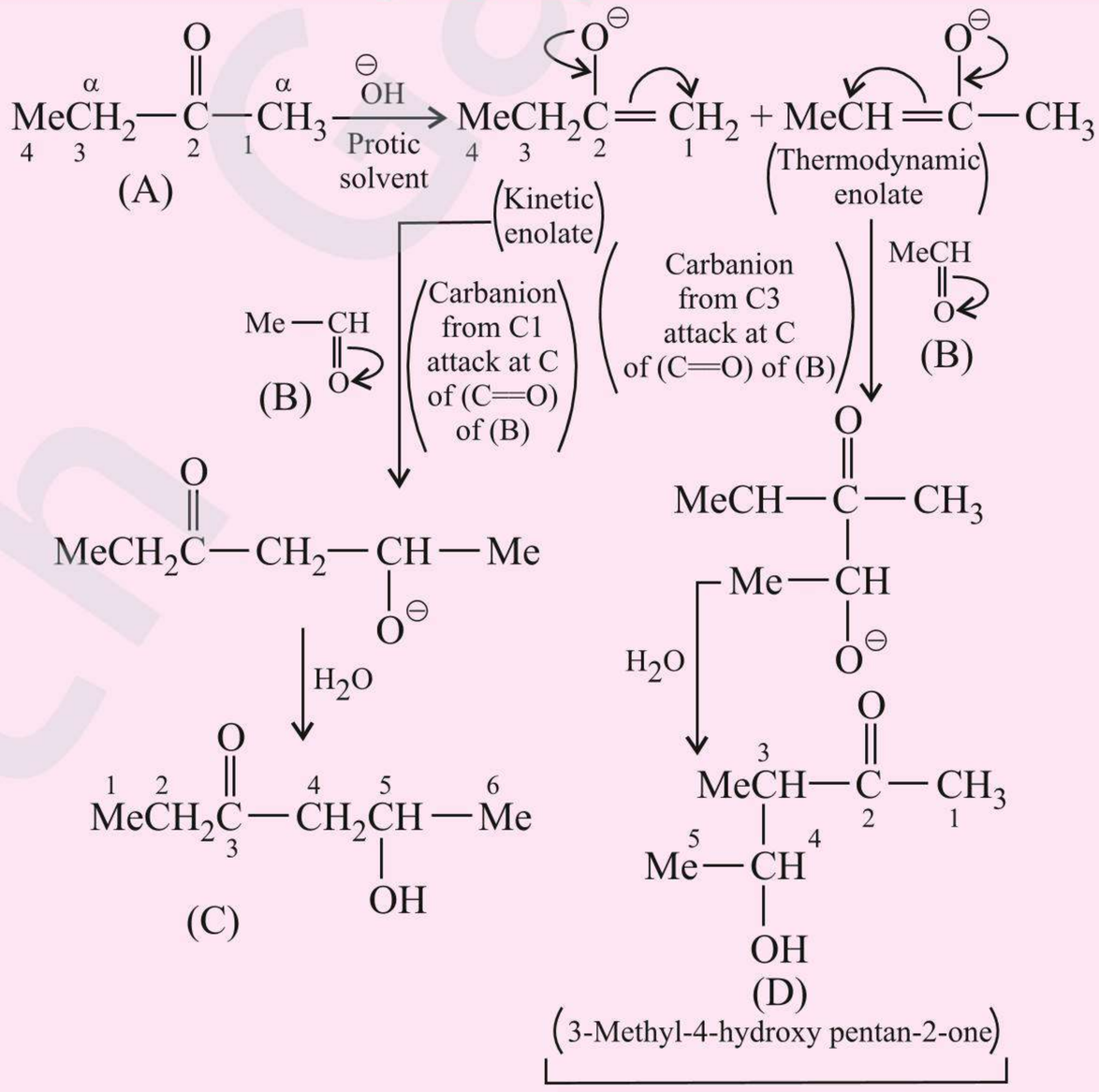
The enolate (II) is usually formed faster, because the removed H atom is less sterically hindered. The enolate (II) is called kinetic enolate and is formed predominantly when the reaction is kinetically or rate controlled.

The enolate (II) is formed faster with strong bulky base LDA, because the strong hindered base rapidly removes the less hindered α-H atom (and there are two H atoms to react).



5.33.2 Directed Aldol Reactions with Lithium Enolates

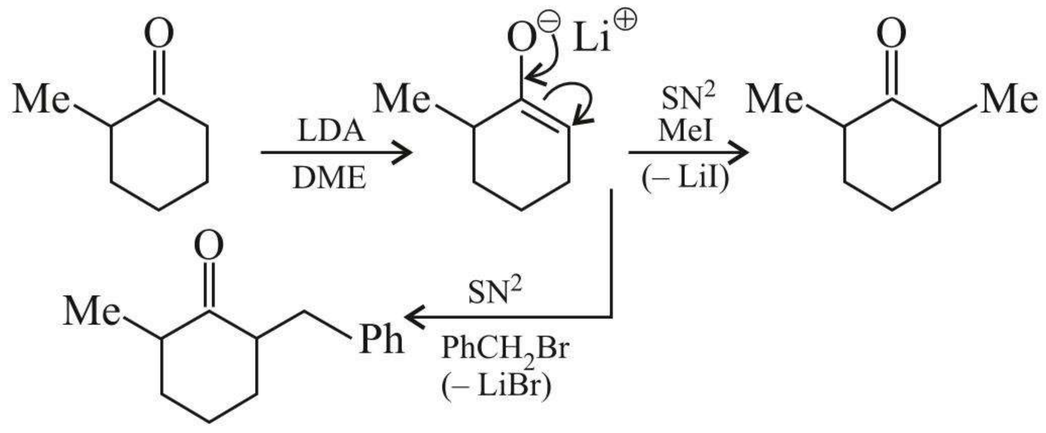
The use of lithium enolate of a ketone as one component and an aldehyde or ketone as the other is the most effective method to prepare a single crossed aldol product. This is called **directed aldol reaction.**

Directed aldol reaction: Crossed aldol reaction using strong bulky base in non-protic solvent (LDA/THF) that produces a single crossed aldol product *via* kinetic enolate.	**Classic aldol reaction:** Crossed aldol reaction using a weak base in protic solvent that produces a mixture *via* both kinetic and thermodynamic enolates.
	

5.33.3 Direct Alkylation of Ketone with LDA via Lithium Enolates

Use of lithium enolates provides a useful method of alkylation of ketone in a regioselective manner.

Lithium enolate of 2-methyl cyclohexanone can be methylated or benzylated with MeI or $PhCH_2Br$ (benzyl bromide), respectively.



Limitations of the reaction:

The reaction proceeds *via* SN^2 mechanism. Since enolate anions are strong bases, the alkylation is feasible only if alkyl halides are 1°, 1° benzylic, and allylic. Further with 2° or 3° RX, the elimination reaction occurs.

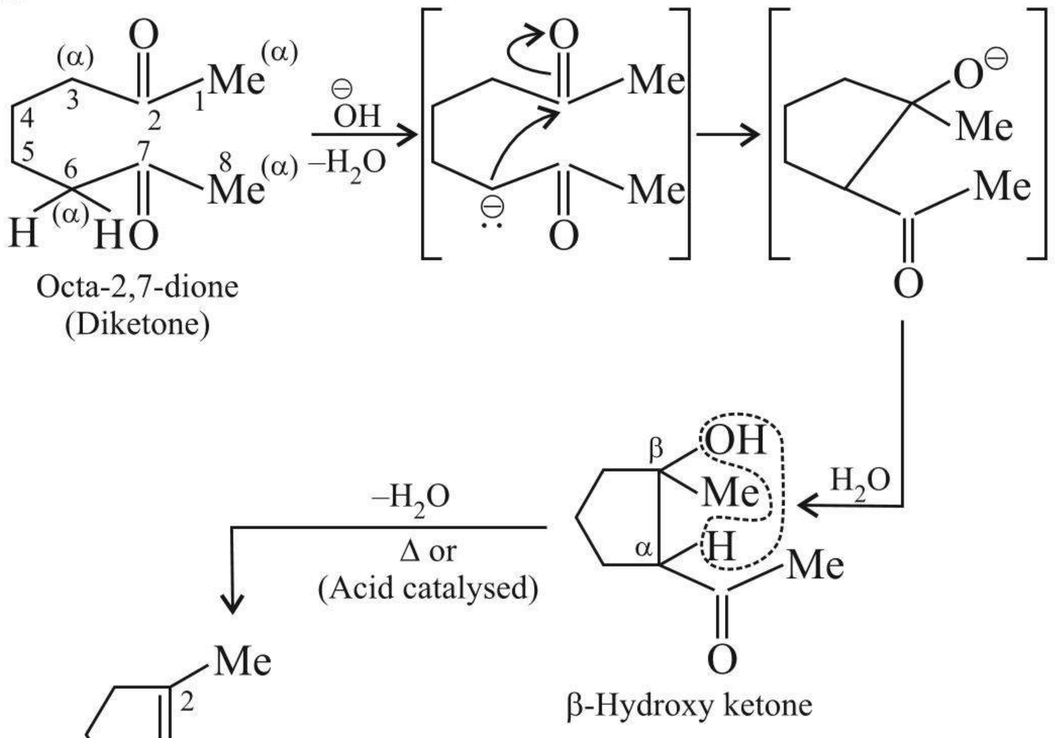
5.34 Intramolecular Aldol Condensation via Cyclisation

When a **dialdehyde** or a **keto aldehyde** or **a diketone** is reacted with weak base, it undergoes intramolecular aldol condensation to give five or six or sometimes larger number of rings.

In case of a keto aldehyde, carbanion of ketone reacts at the C of (CH═O) group; reverse is not feasible because of the greater

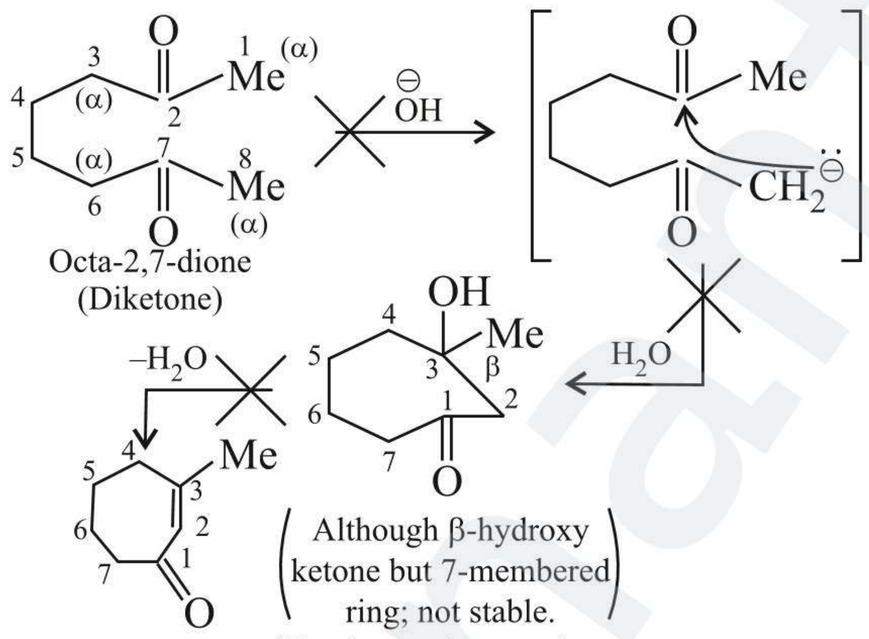
reactivities of aldehydes towards NA (nucleophilic addition) reaction. The (C==O) group of a ketone is less positive and, therefore less reactive towards a nucleophile, since it contains two $\bar{e}$ -releasing (+I) alkyl groups; it is also more sterically hindered, e.g.,

a. i.

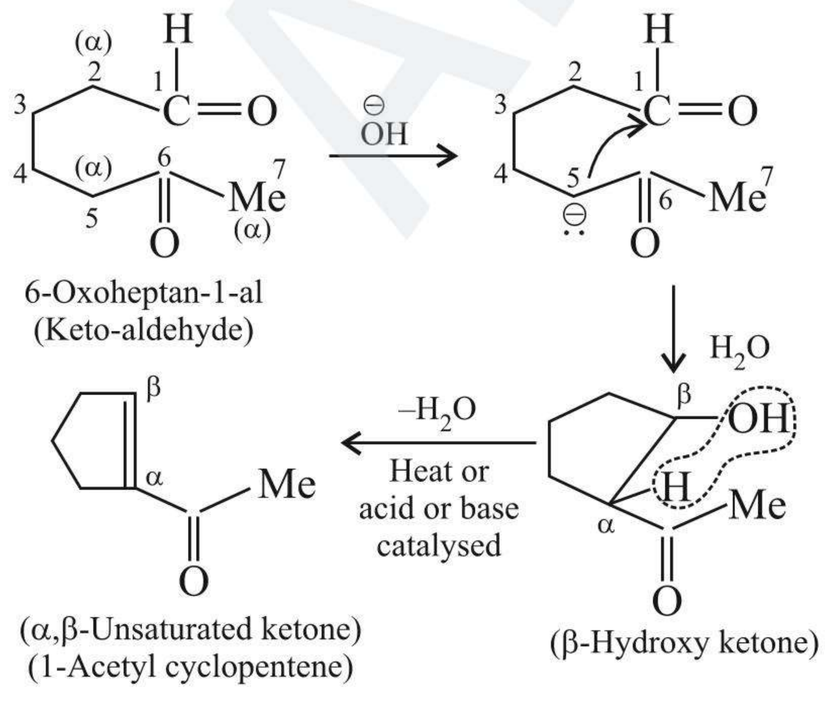


If the carbanion (enolate anion) is formed at C-1 or C-8, the intramolecular alodol condensation should give a seven-membered ring, which is not feasible because the stability order of the ring is six- > five- > seven-membered ring.

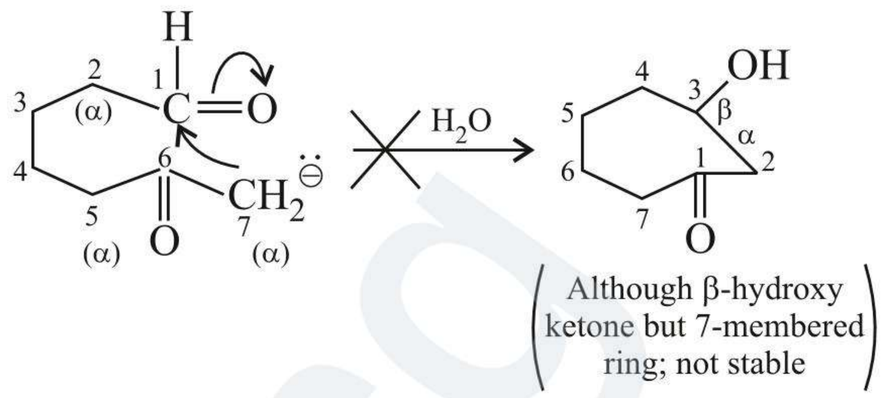
ii.



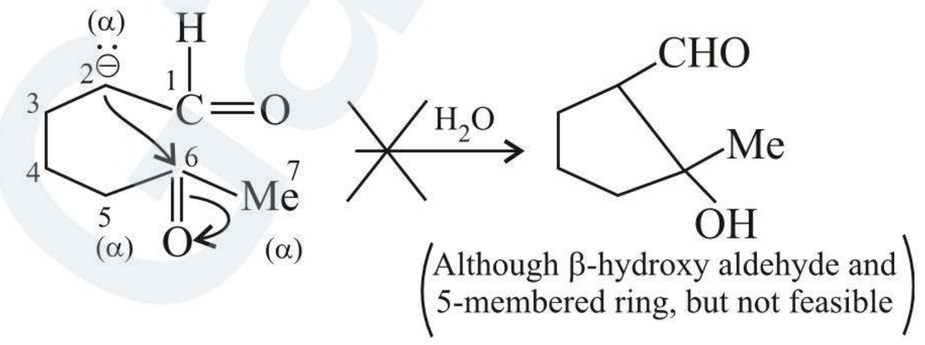
b. i.



ii. If the carbanion formed at C-7 attack at the C-1 of (CHO) group, the seven-membered ring is formed (which is not stable).

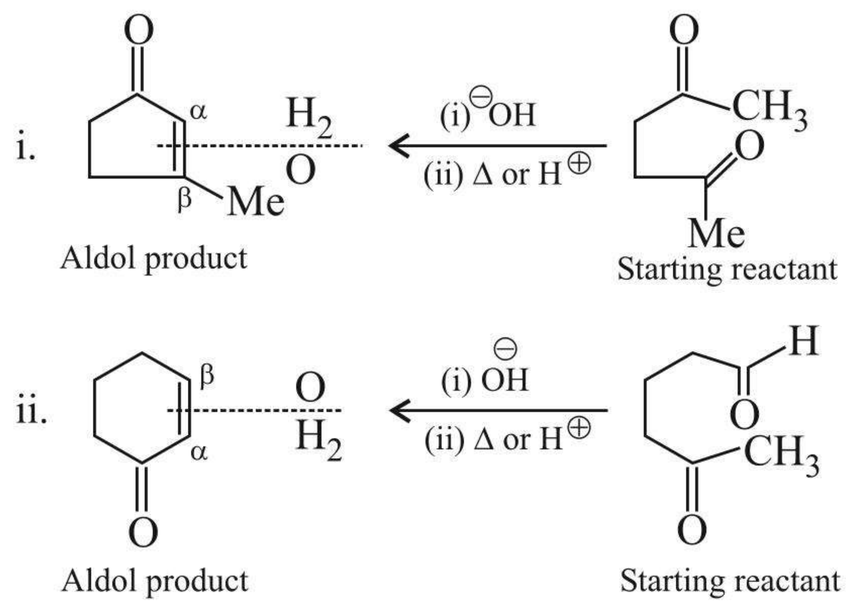


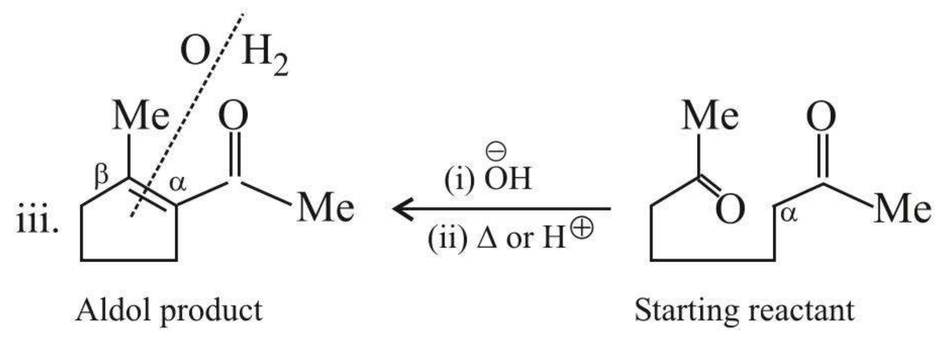
iii. If the carbanion formed at C-2 attack at C-6 of (C═O) group, five-membered ring is formed. This is not feasible, since aldehydes are more reactive towards NA reaction.



5.34.1 Reverse Problem

If the cyclised product of intra-molecular aldol condensation is given, for obtaining the starting reactant, break α,β (C═C) bond by adding H_2O, i.e., H_2 at α-C atom and O at β-C atom, e.g.,





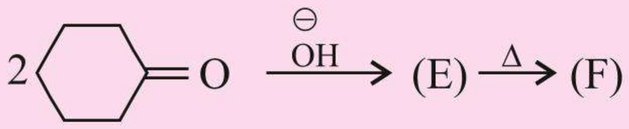
5.34.2 Experimental Conditions to Favour Cyclisation in the Intramolecular Aldol Reaction over Intermolecular Condensation

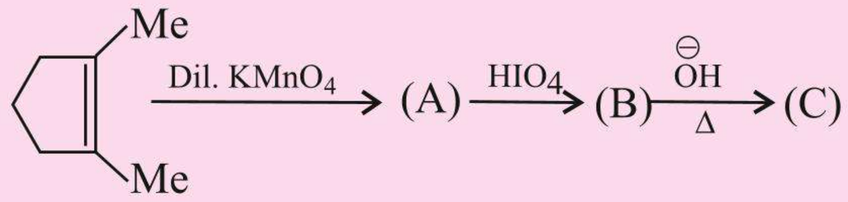
When the concentration of a compound to be cyclised is very low (high dilution technique), the probability of reacting one end of a molecule with the other end of that same molecule is greater than reacting one molecule with a different molecule.

ILLUSTRATION 5.10

1. i. $2CH_3CH_2CHO \xrightarrow{\ominus OH} (A) \xrightarrow{\Delta} (B)$

ii. $2PhCH_2CHO \xrightarrow{\ominus OH} (C) \xrightarrow{\Delta} (D)$

iii. 

2. i. 

ii. A hydrocarbon (A) of the formula C_7H_{12} on ozonolysis gives a compound (B) which undergoes aldol condensation giving 1-acetyl cyclopentene. Identify (A) and (B).

3. Acetone and butan-2-one undergo both self and cross aldol (ketol) condensations to give aldol (ketol) which loses water to give α,β-unsaturated ketones. The number of isomeric α,β-unsaturated ketones formed is:

a. Three **c.** Four

b. Five **d.** Six

4. Give the cyclic intramolecular aldol condensation of the following reactions:

a. Hexane-2,5-dione $\xrightarrow[(ii)\ \Delta]{(i)\ \ominus OH}$

b. Octane-2,7-dione $\xrightarrow[(ii)\ \Delta]{(i)\ \ominus OH}$

c. Nonane-2,8-dione $\xrightarrow[(ii)\ \Delta]{(i)\ \ominus OH}$

5. Identify the reactants that can be and that cannot be synthesised from the compounds given below.

i. PhCH═CHCOCH═CHPh

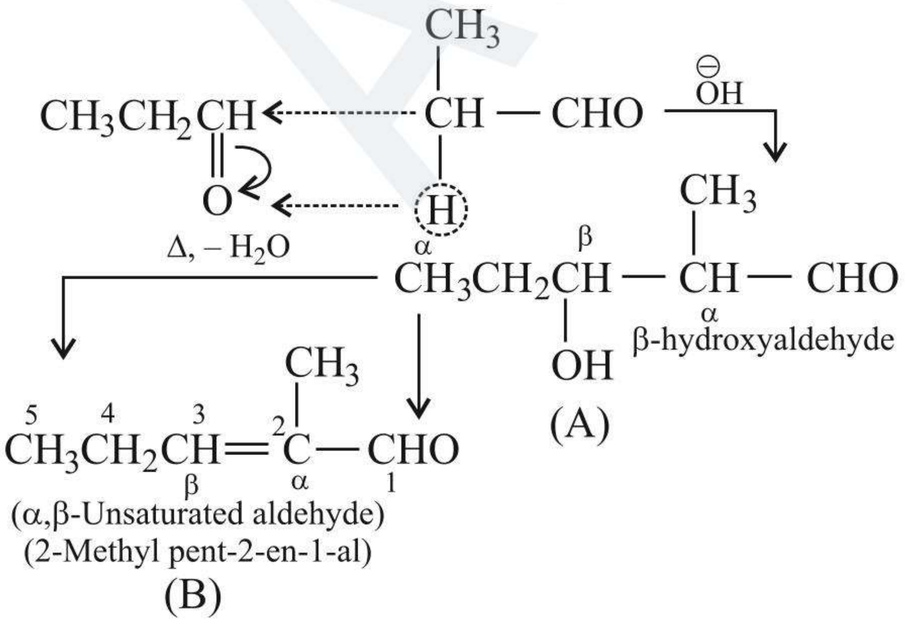
ii. $PhCOCH{=}CH_2$

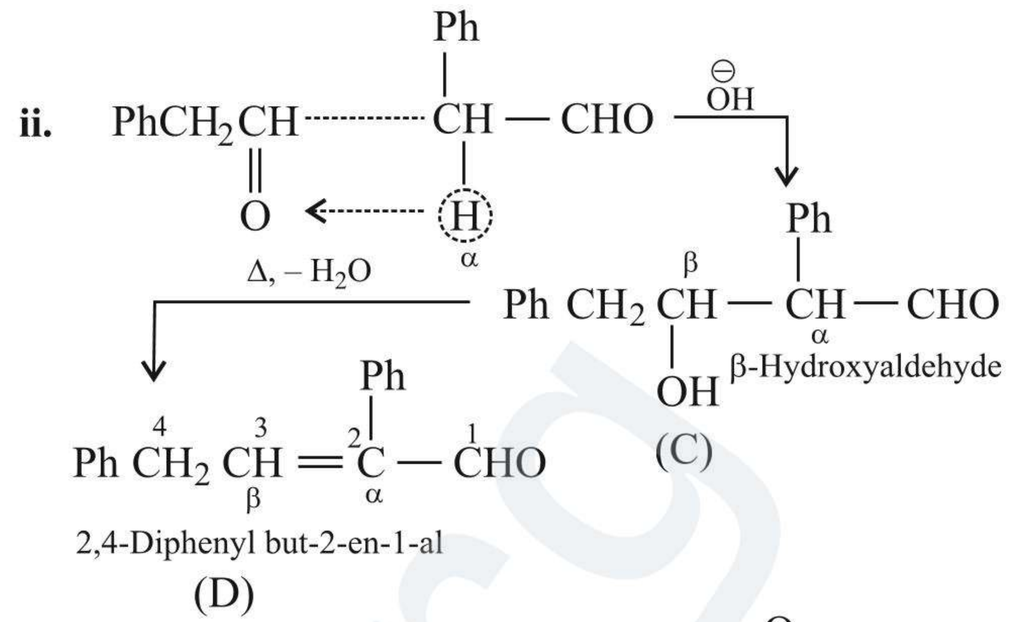
iii. PhCH═CHCH═CHCOMe

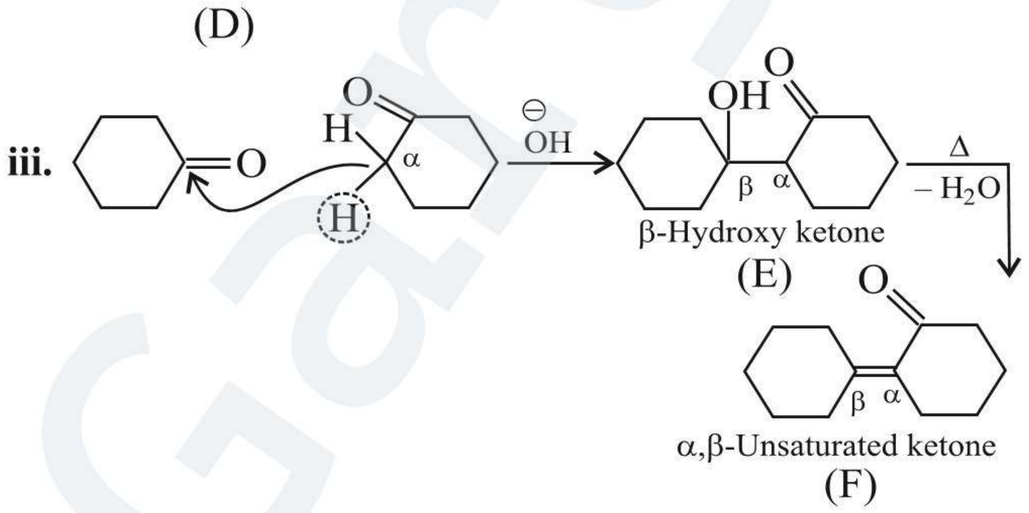
iv. 3-Ethyl-2-methyl cyclohex-2-en-1-one

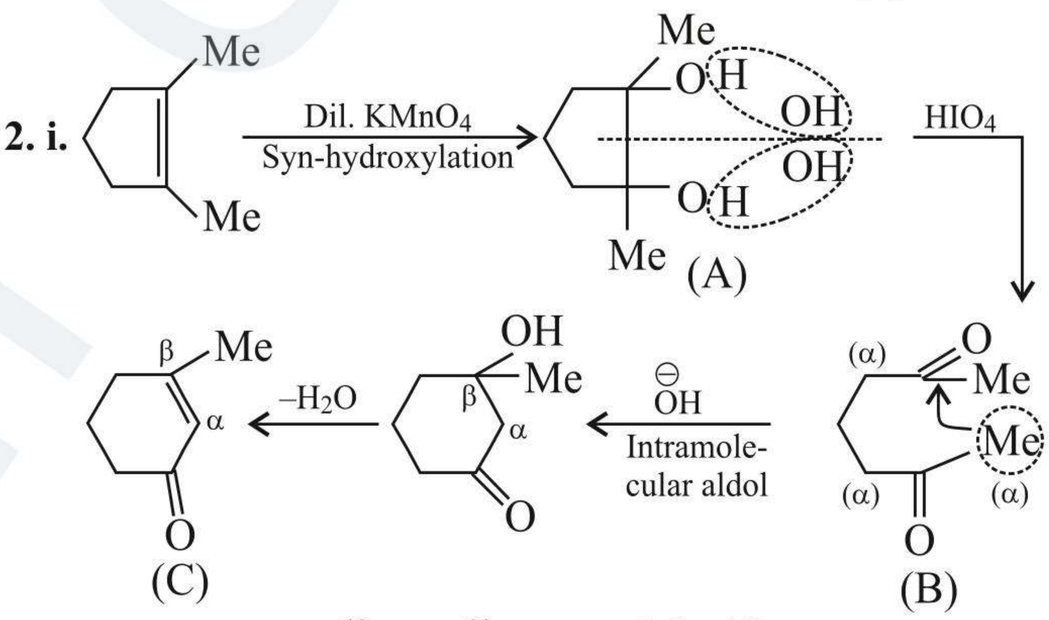
6. Give the mixed aldol product from the reaction of crotonaldehyde ($CH_3CH{=}CH{-}CH{=}O$) with CH_3CHO.

Sol.

1. i. 

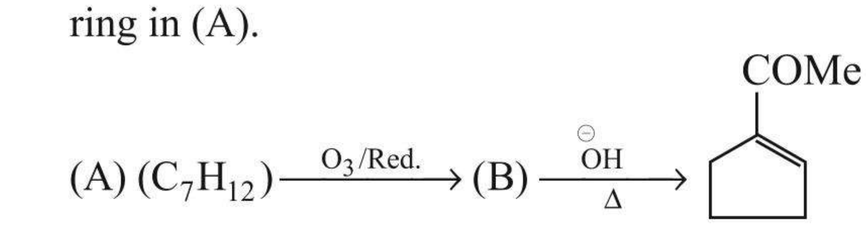
ii. 

iii. 

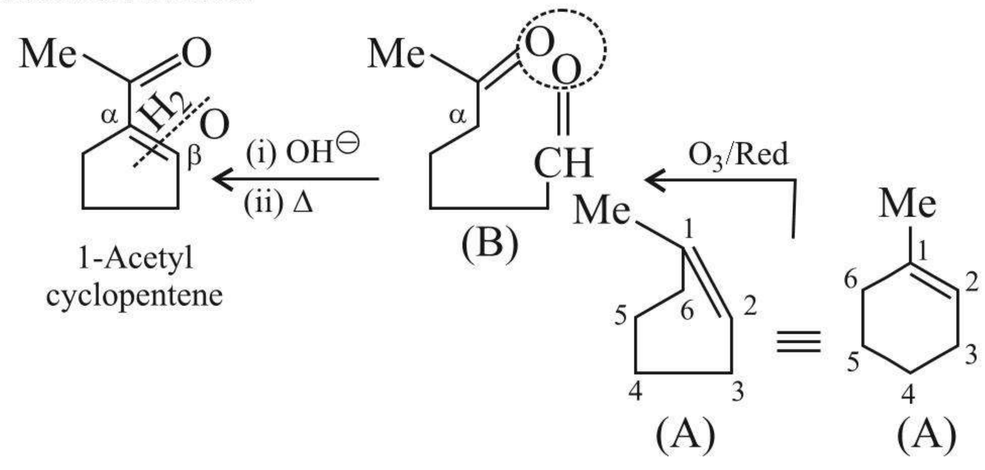
2. i. 

ii. 2 D.U. in A $= \dfrac{(2n_C + 2) - n_H}{2} = \dfrac{16 - 12}{2} = 2°$

Two D.U. in (A) and the ozonolysis of (A) suggest one (C═C) bond; cyclic compound obtained with base suggests ring in (A).

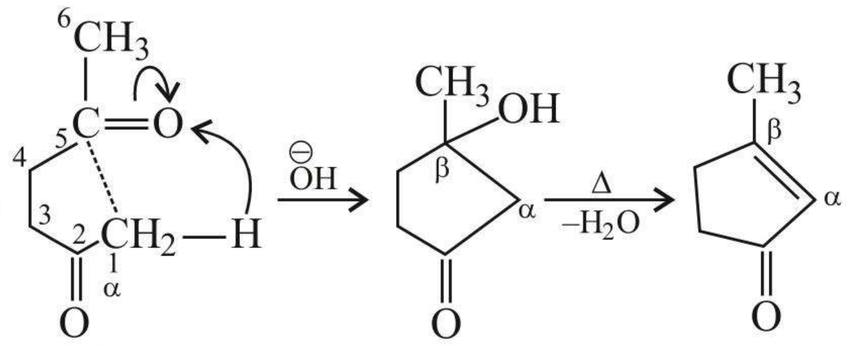


Proceed reverse:

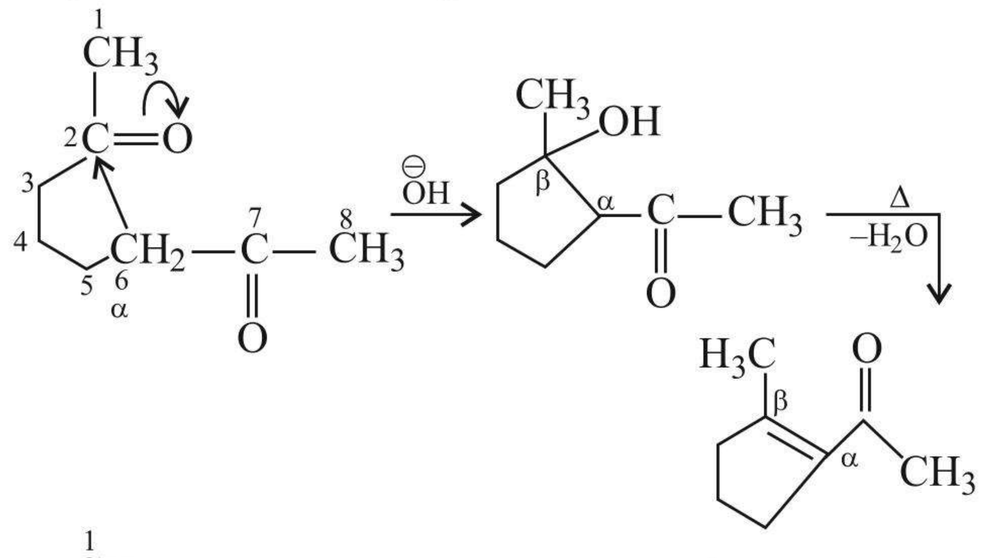


3. d. Three self and three crossed aldol condensation products: Butan-2-one (unsymmetrical ketone) has two types of dissimilar α-H atoms ($\overset{\alpha}{Me}CO\overset{\alpha'}{CH_2}Me$), and acetone (symmetrical ketone) has only one type of similar α-H atoms ($\overset{\alpha}{Me}CO\overset{\alpha}{Me}$).

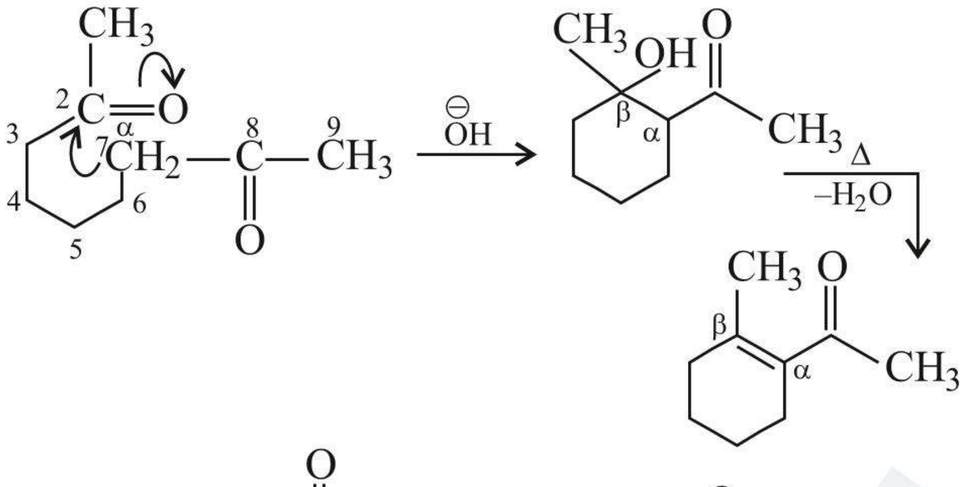
4. a.



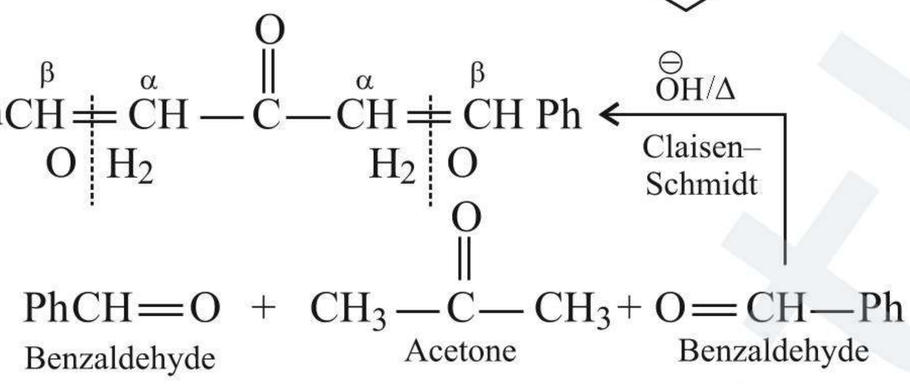
b.



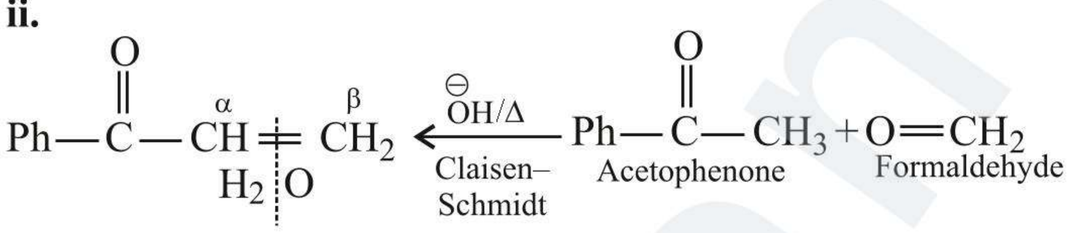
c.



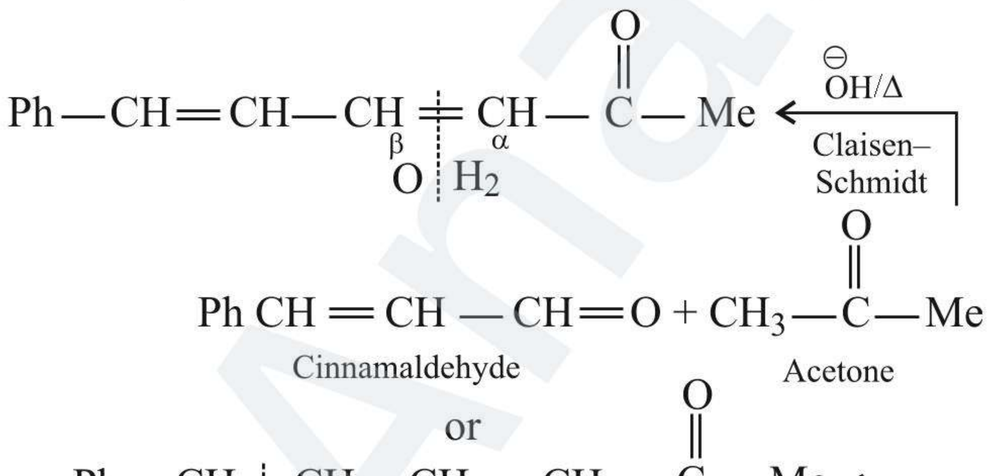
5. i.



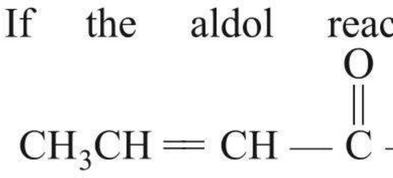
ii.



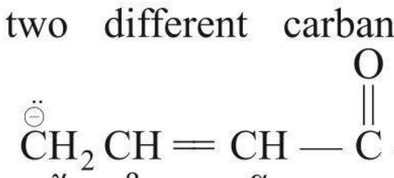
iii.



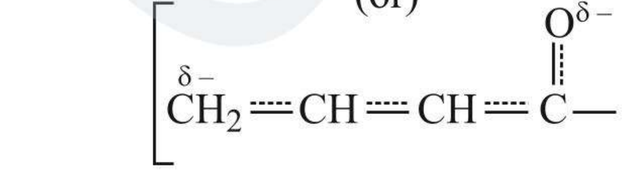
If the aldol reaction of PhCH═O (I) with



(II) occurs, two different carbanions (enolate anions) can form

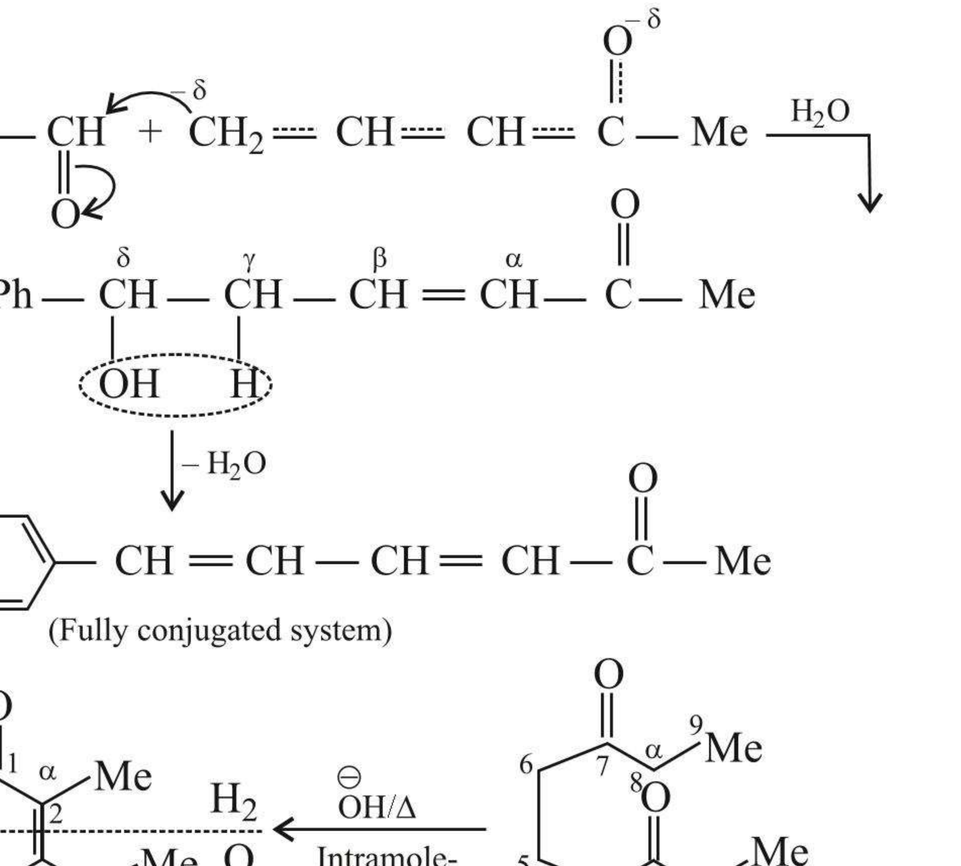


(III) and



(IV).

The carbanion (enolate anion) (III) is formed more easily than (IV). The carbanion (III) formed by the removal of γ-H of (II) with base is delocalised to O through the conjugated system giving a stable carbanion enolate.



This anion (III) adds to the (C═O) of PhCH == O (I) to give δ-hydroxy alcohol which rapidly loses H_2O to give the product that is triply conjugated and also is extended- conjugated with Ph group.

iv.

6.

Limitation of the reaction:

Sorbic aldehyde has acidic H (at C-6) and hence can react with more CH_3CHO to give polymeric compound.

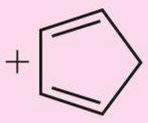
ILLUSTRATION 5.11

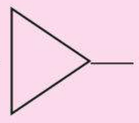
Complete the following reactions:

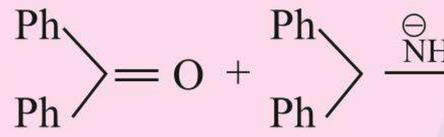
a. $PhCHO + CH_3NO_2 \xrightarrow[\Delta]{\ominus OH} (A)$

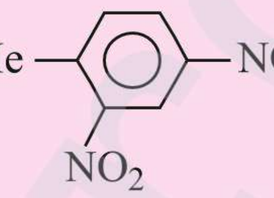
b. $Me_2CO + CHCl_3 \xrightarrow{\ominus OH} (B)$

c. $PhCHO + CH_3C \equiv N \xrightarrow{\ominus NH_2} (C)$

d. $Me_2CO +$  $\xrightarrow[\Delta]{\ominus OH} (D)$

e. $PhCHO +$  $\xrightarrow[\Delta]{\ominus OH} (E)$

f. 

g. $PhCHO +$  $\xrightarrow{\dot{N}HR_2} (G)$

Sol.

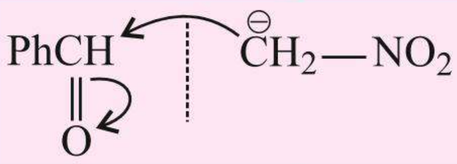
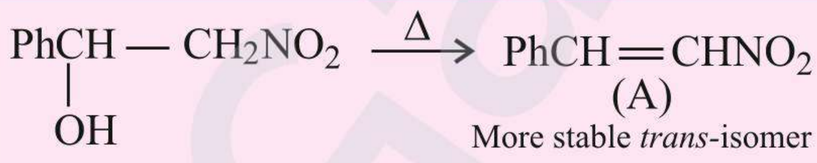
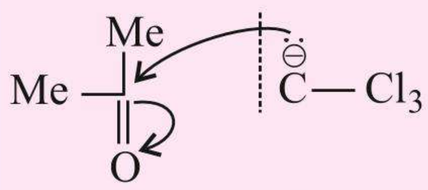
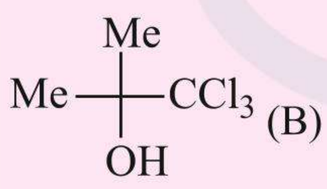
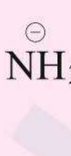
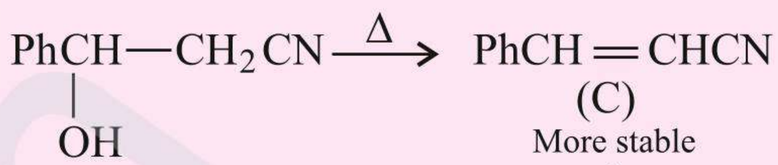
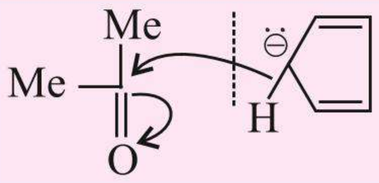
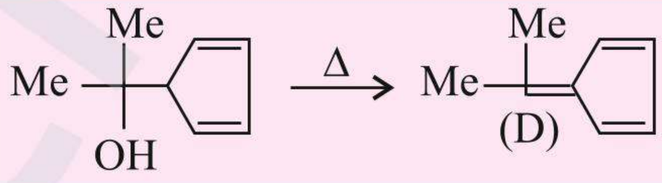
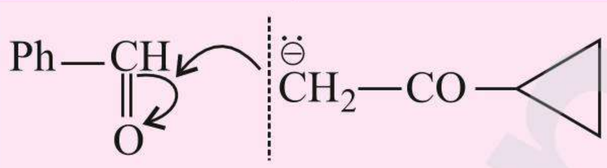
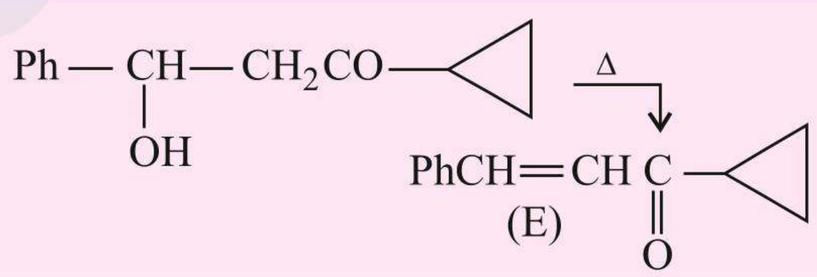
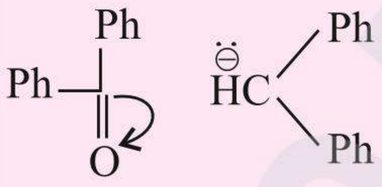
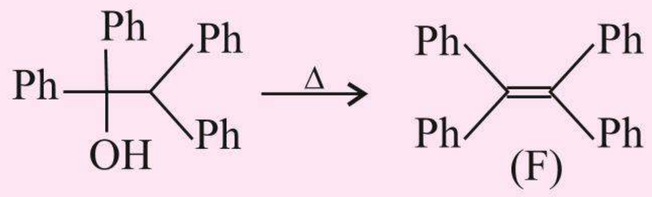
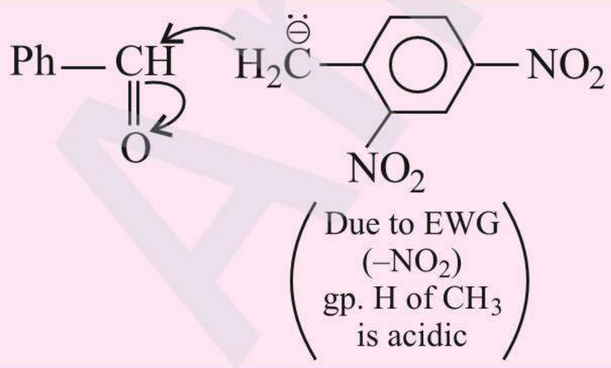
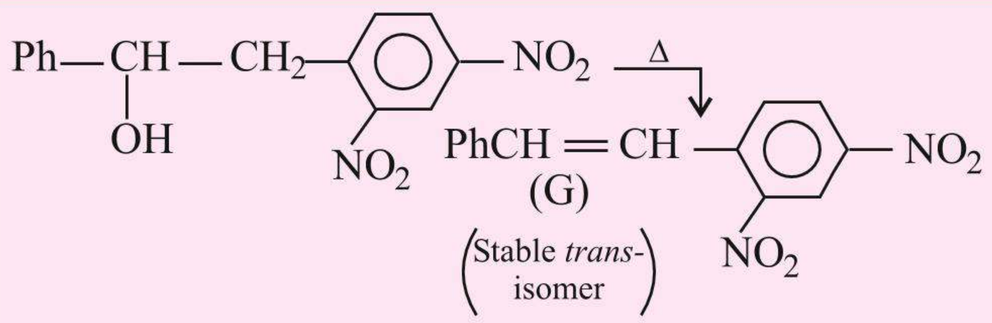
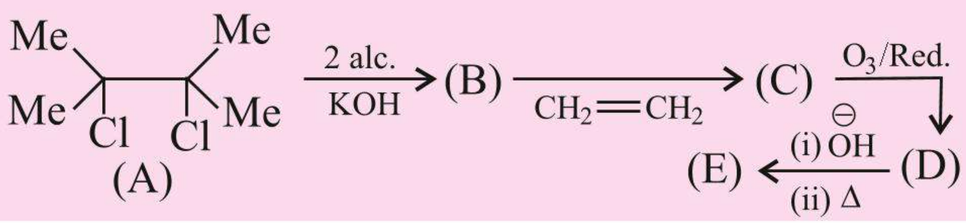
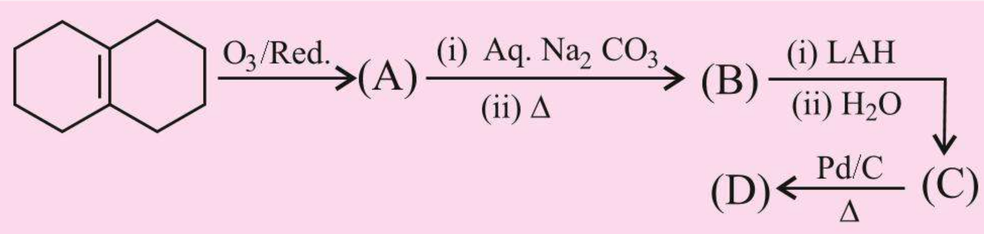
S.No.	Acceptor	Carbanion	Base	Product
a.				 (A) More stable *trans*-isomer
b.				 (B)
c.				 (C) More stable *trans*-isomer
d.				 (D)
e.				 (E)
f.				 (F)
g.	 Due to EWG ($-NO_2$) gp. H of CH_3 is acidic			 (G) Stable *trans*-isomer

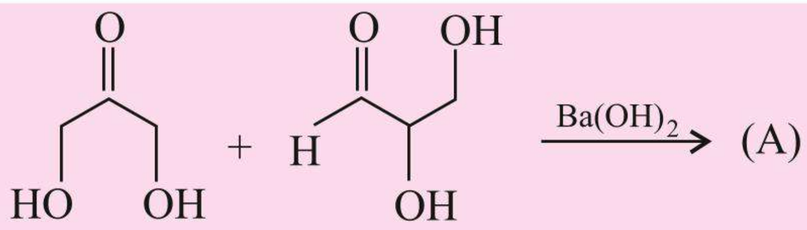
ILLUSTRATION 5.12

Complete the following reactions:

a. 

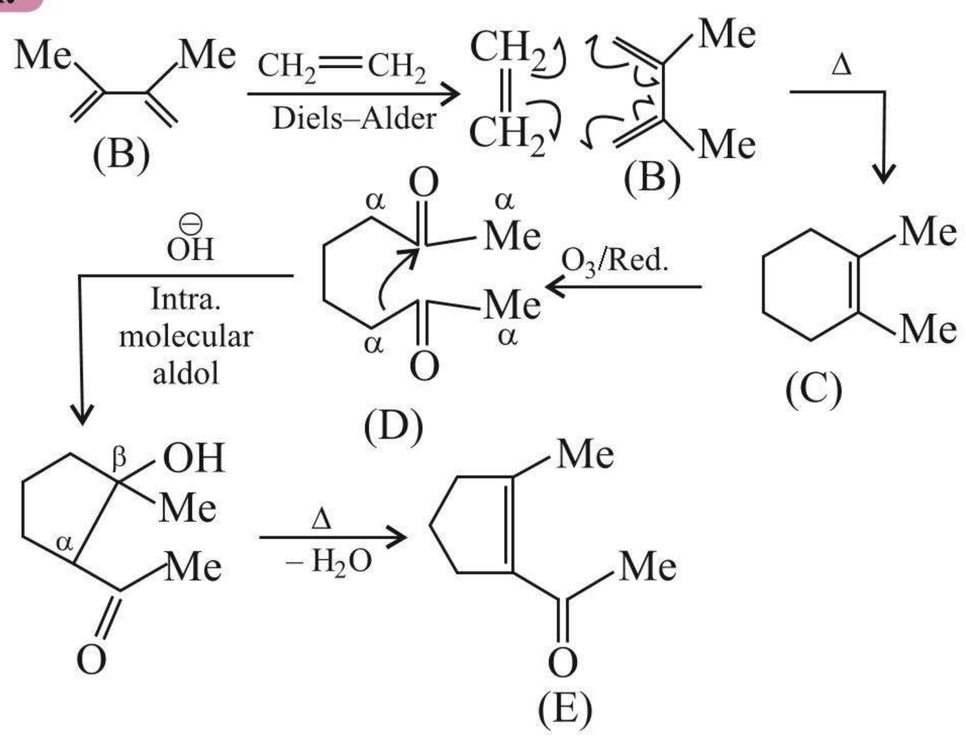
b. 

c.

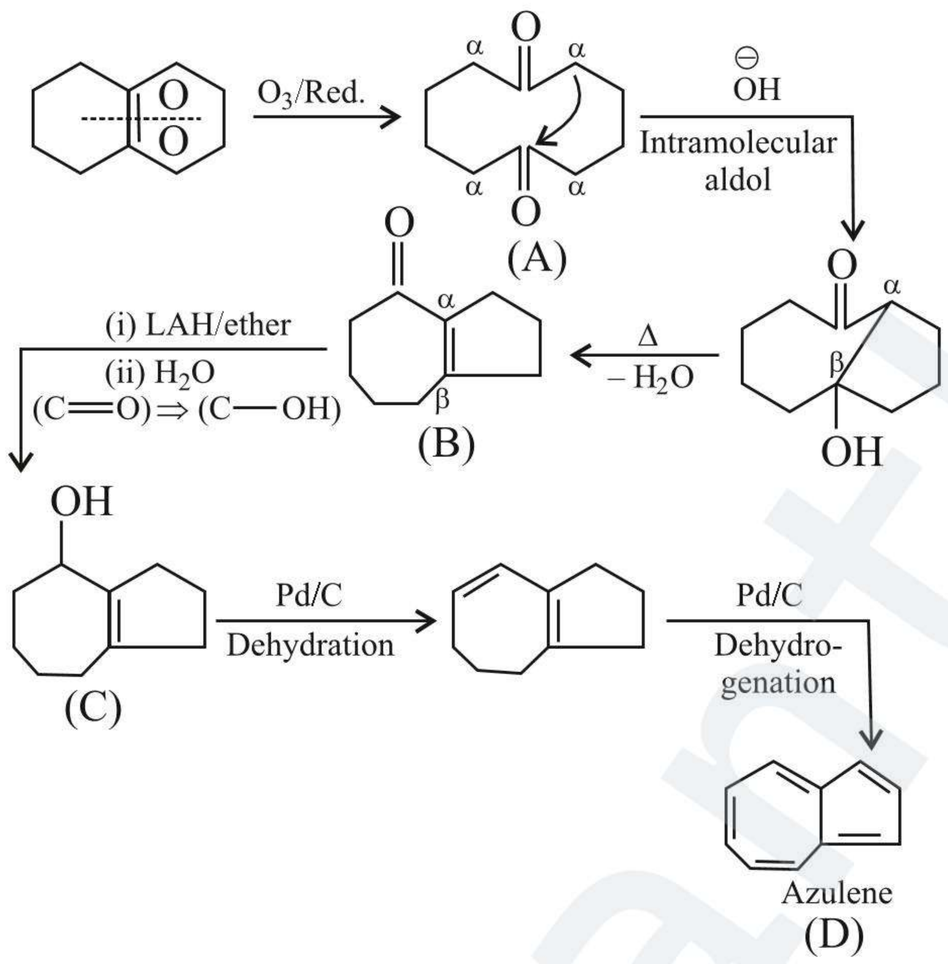


Sol.

a.



b.



c. Aldehydes are better acceptors than ketones. Therefore, carbanion formed by the removal of α-H atom of ketone with base adds to the C atom of (CH═O) group to give β-hydroxy ketone.

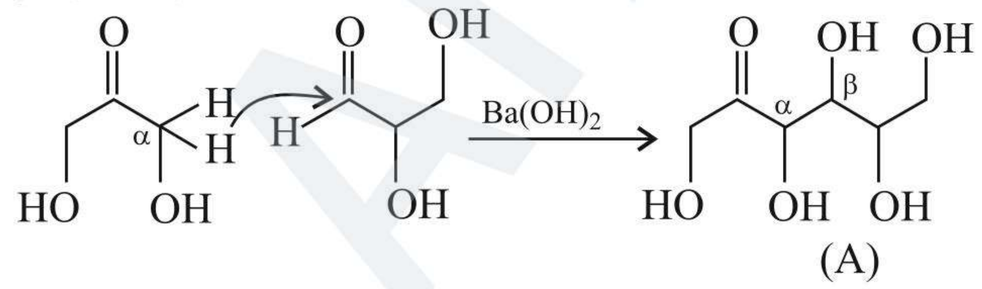
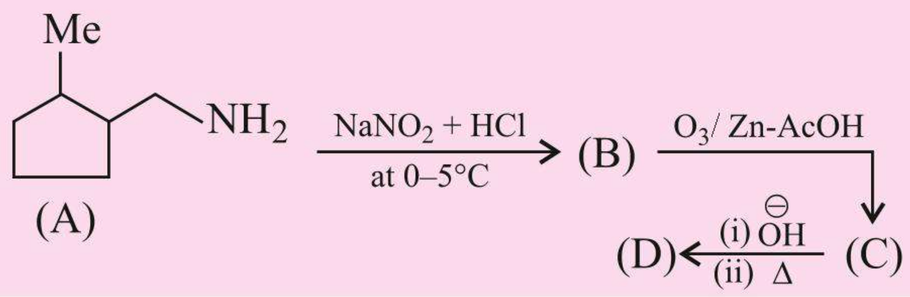


ILLUSTRATION 5.13

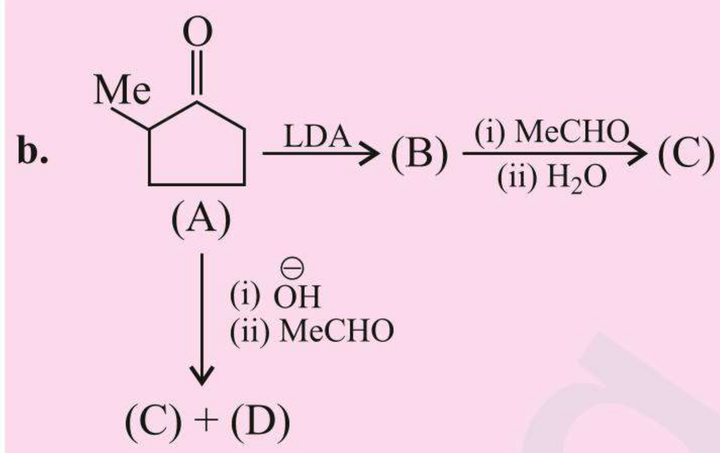
Complete the following reactions:

a.

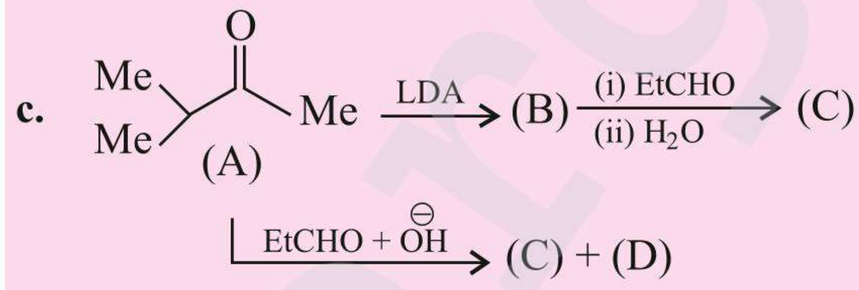


b. LDA (a bulky strong base) abstracts less hindered α-H atom to form lithium enolate which adds to C of (CH═O) group, to form β-hydroxy ketone, limiting to only one crossed aldol product. On the other hand, with a weak base (NaOH), two crossed aldol products are formed.

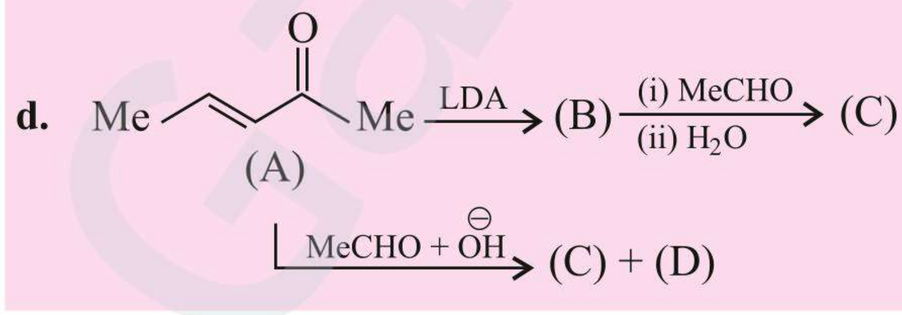
b.



c.

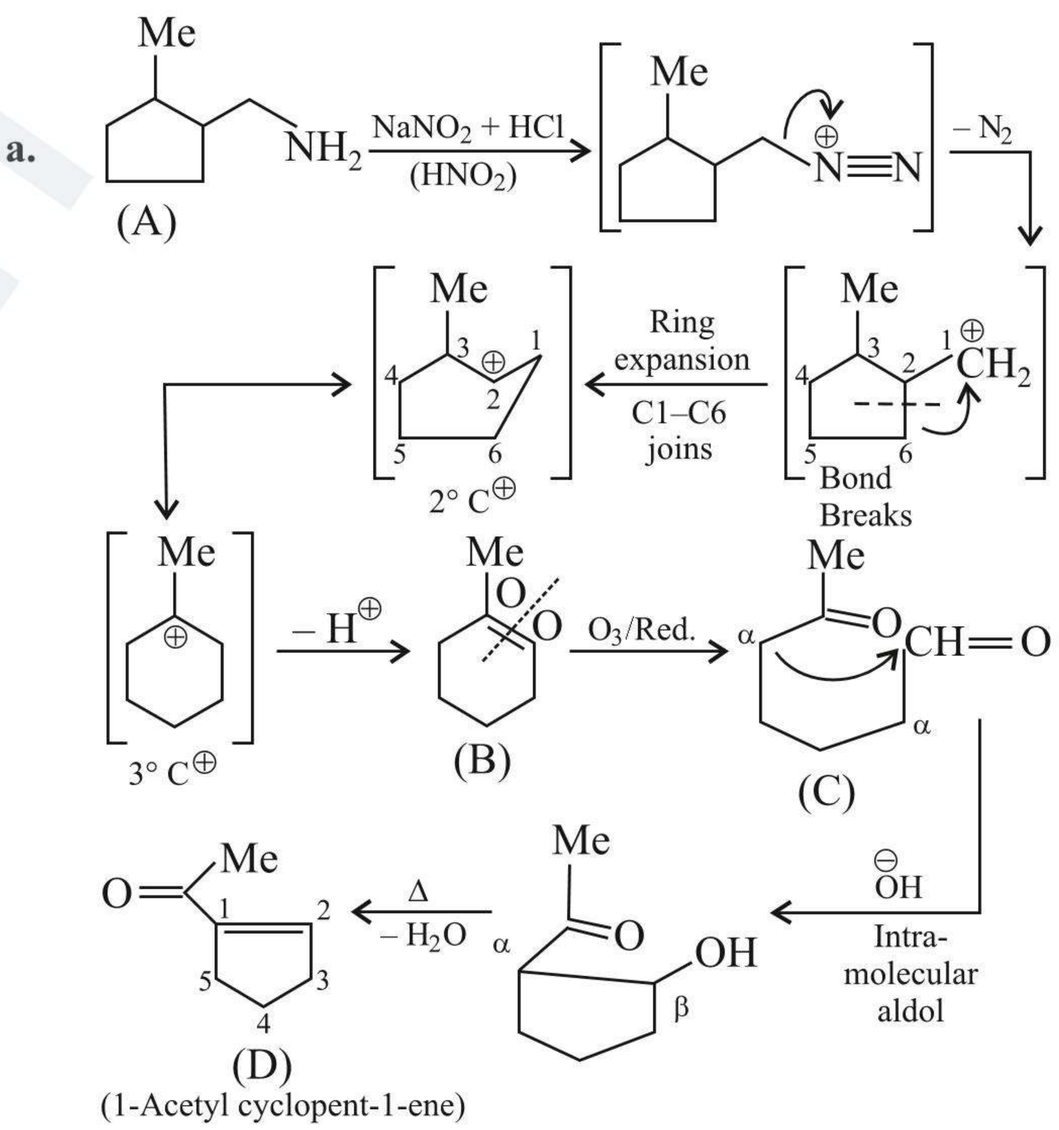


d.



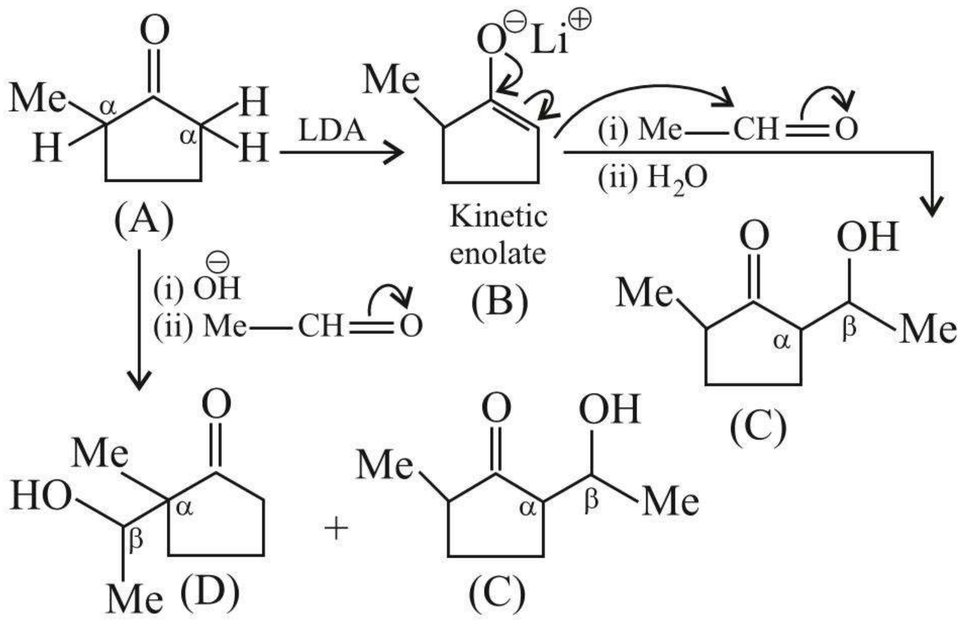
Sol.

a.

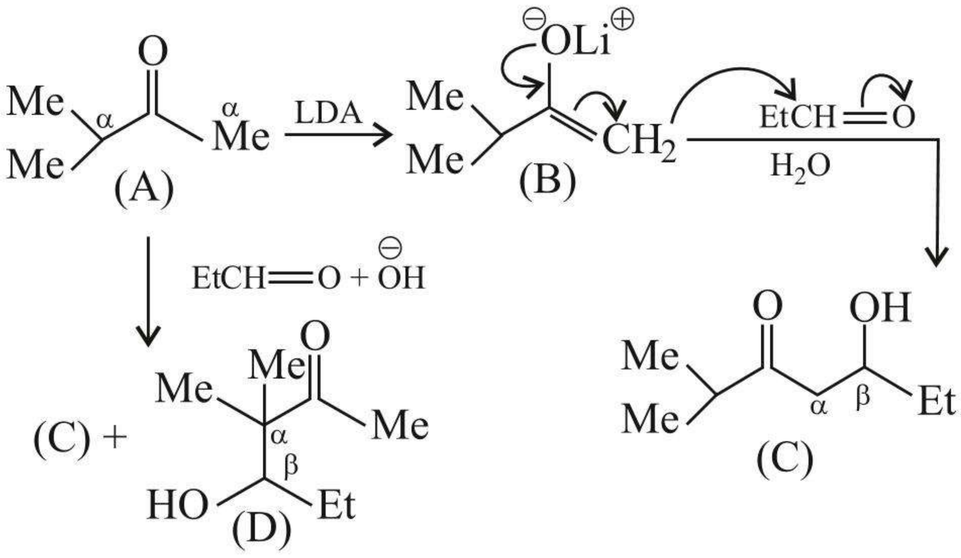


(1-Acetyl cyclopent-1-ene)

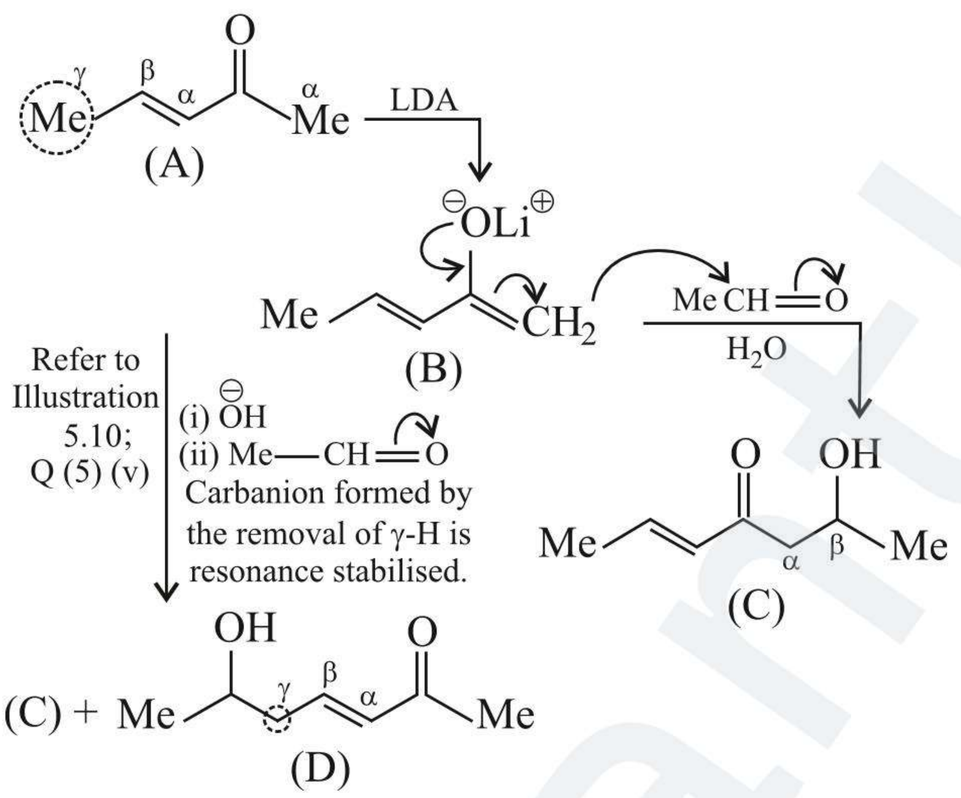
b. LDA (a bulky strong base) abstracts less hindered α-H atom to form lithium enolate which adds to C of (CH═O) group, to form β-hydroxy ketone, limiting to only one crossed aldol product. On the other hand, with a weak base (NaOH), two crossed aldol products are formed.

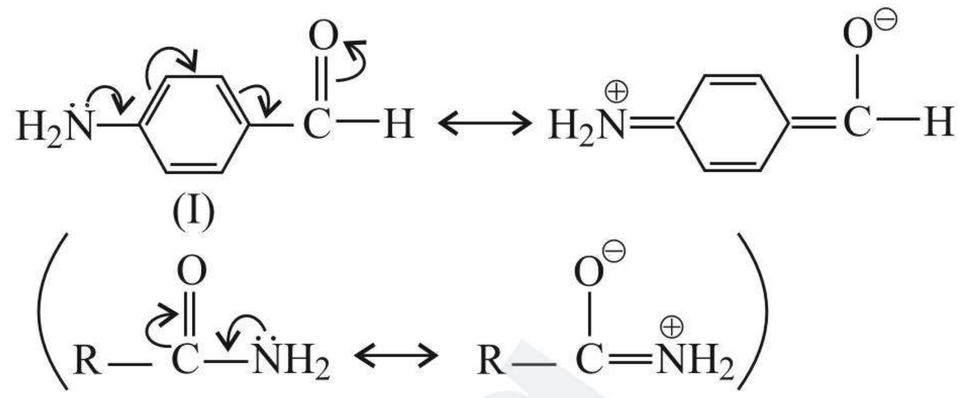


c.

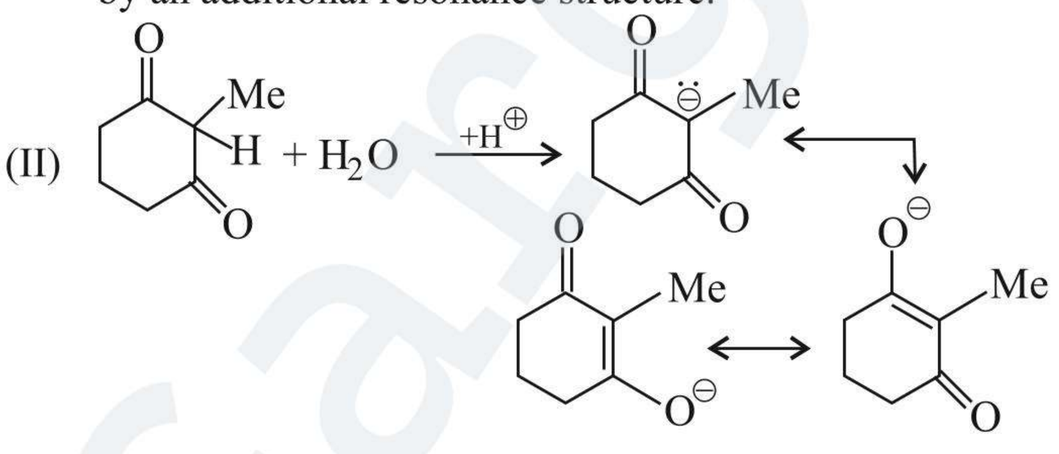


d.





b. Here, (II) is more acidic because its anolate ion is stabilised by an additional resonance structure.



c.

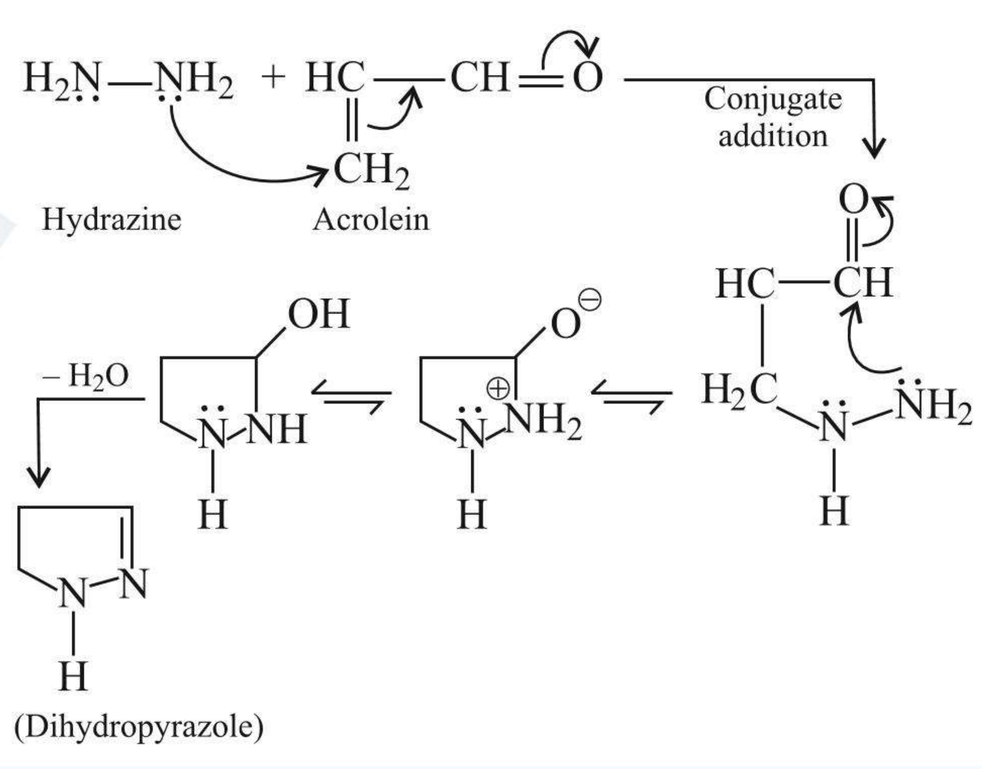
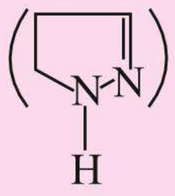


ILLUSTRATION 5.14

Explain:

a. *p*-Aminobenzaldehyde (I) does not show nucleophilic addition reaction and Cannizzaro reaction.

b. Which is more acidic and why: (I) cyclohexanone or (II) 2-methyl cyclohexan-1,3-dione?

c. When acrolein (CH_2=CH—CHO) reacts with hydrazine ($\ddot{N}H_2\ddot{N}H_2$), dihydropyrazole  is formed. Give the mechanism of the reaction.

Sol.

a. Due to resonance stabilisation, there is no true (C=O) bond present in (I) and it behaves as an amide.

5.35 CANNIZZARO REACTION

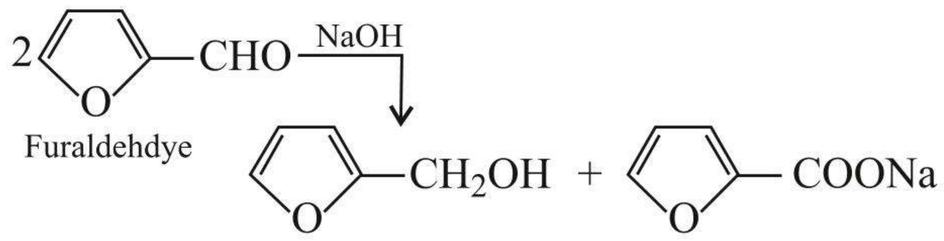
Two molecules of the same aldehyde lacking α-H atom undergo disproportionation or redox reaction in the presence of strong base to give a molecule of alcohol and a molecule of the salt of an acid, e.g.,

i. $HCHO + HCHO \xrightarrow{NaOH} \underset{\text{Methanol}}{H—CH_2OH} + \underset{\text{Sod. formate}}{HCOONa}$

ii. $Ph—CHO + Ph—CHO \xrightarrow{KOH} \underset{\text{Benzyl alcohol}}{Ph—CH_2OH} + \underset{\text{Pot. benzoate}}{Ph—COOK}$

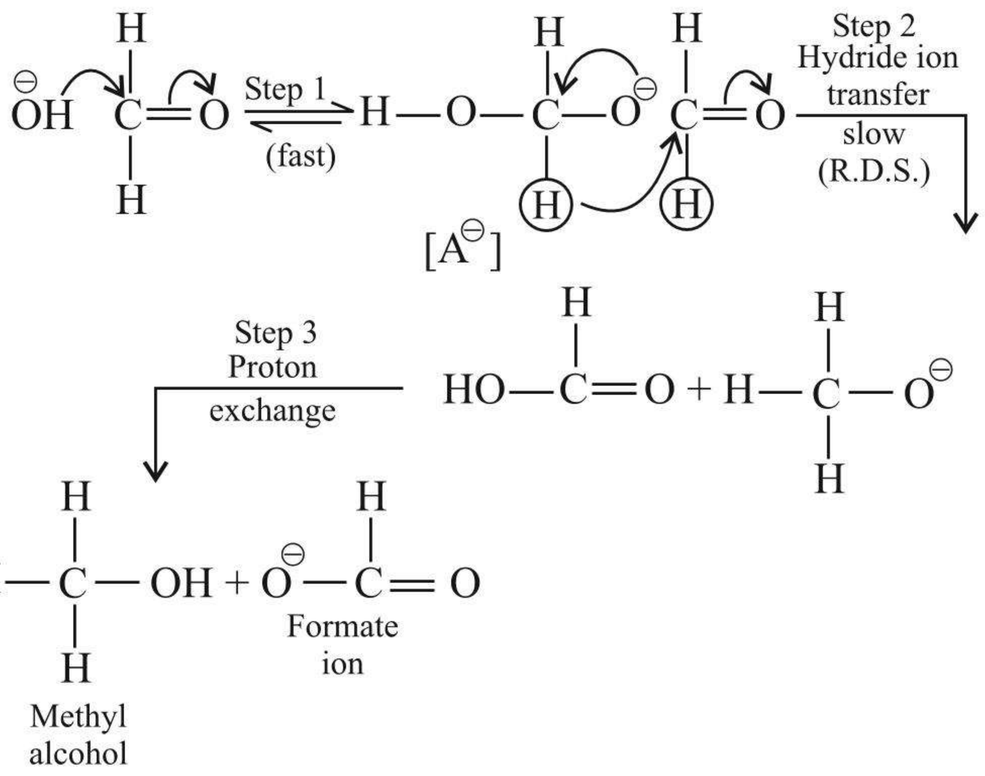
iii. $2Me_3C—CHO \xrightarrow{NaOH} 2Me_3C—CH_2OH + Me_3C—COONa$

iv.



5.35.1 Mechanism

[Takes place by $H^{\ominus}$ (hydride ion transfer) when the concentration of the base is low.]



i. Rate = K[HCHO] [$A^{\ominus}$]

ii. $K_{eq} = \dfrac{[A^{\ominus}]}{[HCHO][\overset{\ominus}{O}H]}$

iii. $[A^{\ominus}] = K_{eq}$ [HCHO] [$\overset{\ominus}{O}H$]

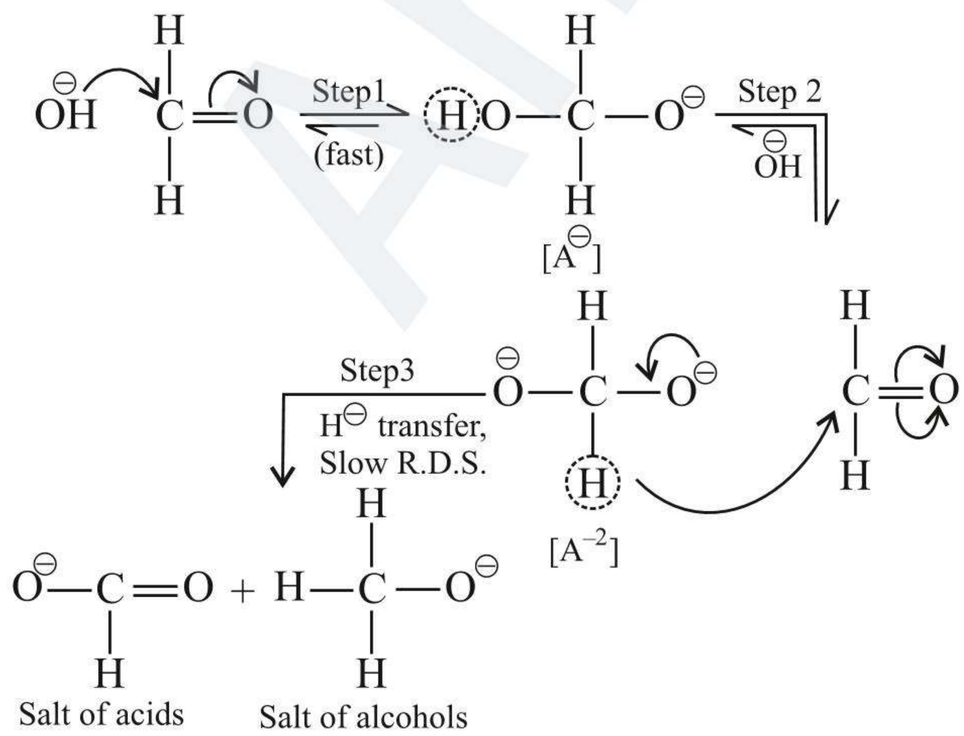
Substituting the value of [$A^{\ominus}$] in equation (i), we get

Rate = $K.\ K_{eq}$ [HCHO] [HCHO] [$\overset{\ominus}{O}H$]

$= K'$ [HCHO]^2 [$\overset{\ominus}{O}H$]

Hence the Cannizzaro reaction in low concentration of a strong base is bimolecular with third-order kinetics, second-order w.r.t. aldehyde, and first-order w.r.t. $\overset{\ominus}{O}H$ ions.

5.35.2 Mechanism (Also Takes Place by $H^{\ominus}$ Transfer) When the Concentration of Base is High



Subsequently, the alkoxide ion acquires a proton from the solvent.

$$CH_3O^{\ominus} \xrightarrow[\text{from solvent}]{H_2O} CH_3OH + \overset{\ominus}{O}H$$

i. Rate = K [HCHO] [A^{-2}]

ii. $K_{eq2} = \dfrac{[A^{-2}]}{[A^{\ominus}][\overset{\ominus}{O}H]}$

iii. $[A^{-2}] = K_{eq2}$ [$A^{\ominus}$] [$\overset{\ominus}{O}H$]

iv. $K_{eq1} = \dfrac{[A^{\ominus}]}{[HCHO][\overset{\ominus}{O}H]}$

v. $[A^{\ominus}] = K_{eq1}$ [HCHO] [$\overset{\ominus}{O}H$]

[Substituting the value of [$A^{\ominus}$] in equation (iii).]

vi. $[A^{-2}] = K_{eq1}K_{eq2}$ [HCHO] [$\overset{\ominus}{O}H$][$\overset{\ominus}{O}H$]

$= K'_{eq}$ [HCHO] [$\overset{\ominus}{O}H$]^2

Substituting the value of [A^{-2}] from equation (vi) in equation (i).

$\therefore$ Rate = $K\,K'_{eq}$ [HCHO] [HCHO] [$\overset{\ominus}{O}H$]^2

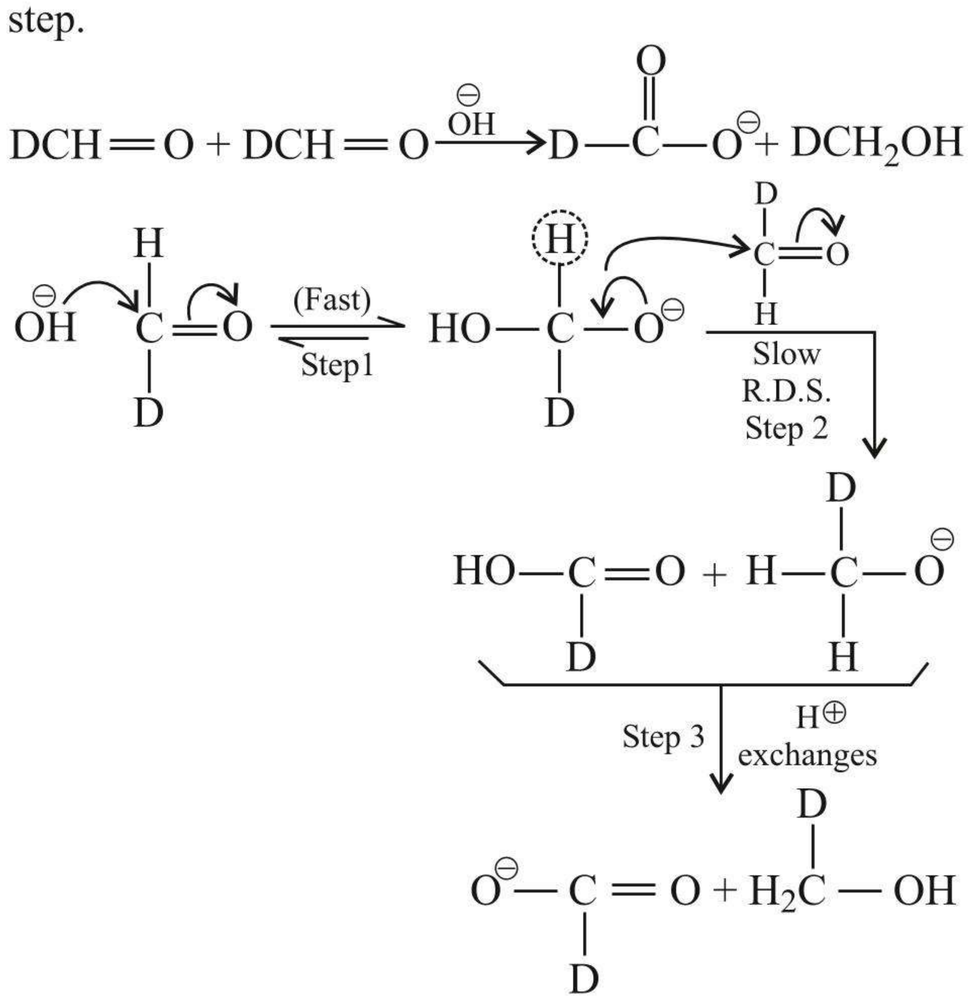
$= K'$ [HCHO]^2 [$\overset{\ominus}{O}H$]^2

Hence, the Cannizzaro reaction in high concentration of a strong base is bimolecular with fourth-order kinetics, second-order w.r.t. aldehyde, and second order w.r.t. $\overset{\ominus}{O}H$ ions.

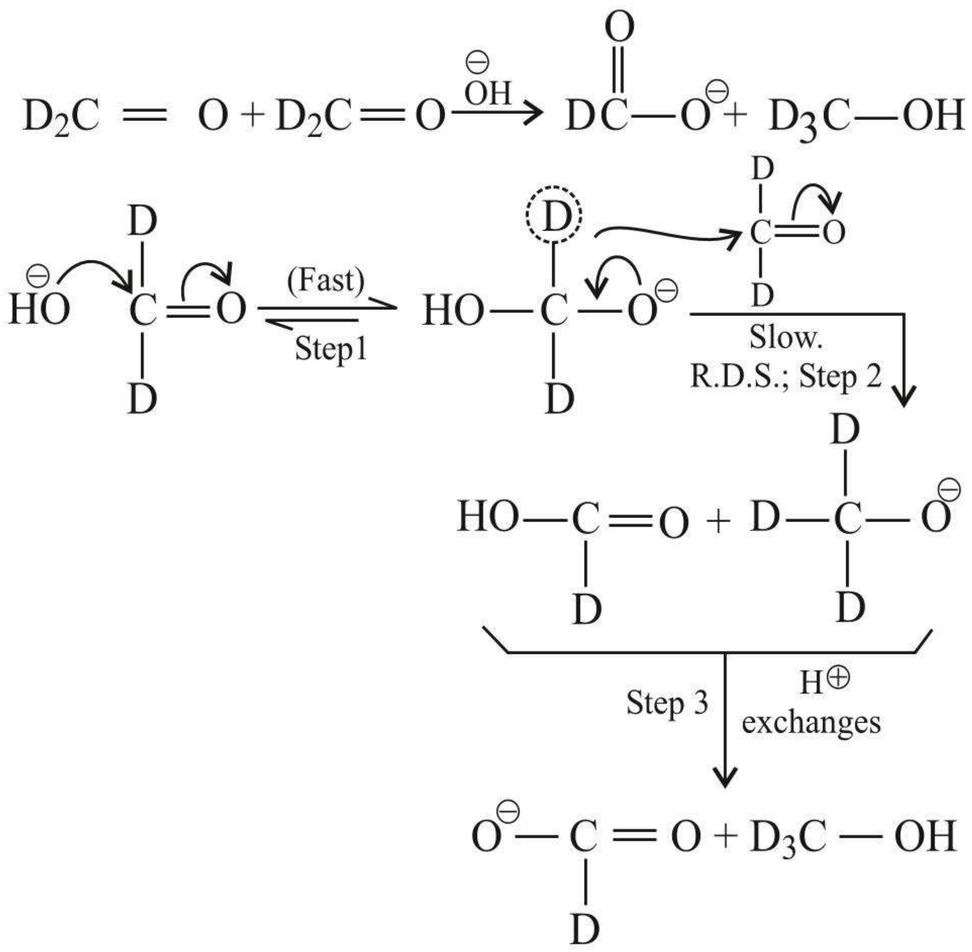
5.35.3 Cannizzaro Reaction in Deuterium Containing Aldehyde

If aldehydes (with no α-H atom) contain one (C—H) and one (C—D) bond:

i. (C—H) bond is weaker than (C—D) bond, so $H^{\ominus}$ transfer takes place rather than $D^{\ominus}$ transfer in slow, rate-determing step.



ii. If the aldehyde (with no α-H) contains both (C—D) bonds, $D^{\ominus}$ transfer takes place.

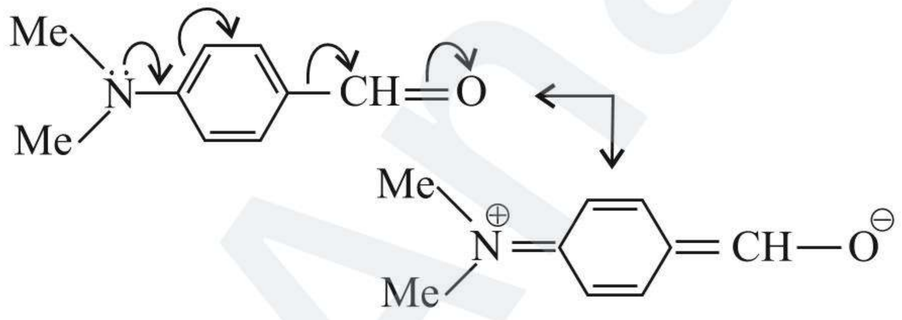


5.35.4 When the Undeuterated Aldehyde (CH_2=O) Is Reacted with NaOH Dissolved in D_2O

The fact that $H^{\ominus}$ ion is directly transferred from one molecule of aldehyde to the other (and does not become free in solution) has been proved by the observation that the recovered alcohol does not contain deuterium when the reaction is performed in the presence of D_2O. The products obtained are $HCOO^{\ominus}$ and CH_3OH.

5.35.5 Limitation of Cannizzaro Reaction

i. It is clear from the mechanism that the reaction depends on the nucleophilic attack on the (C=O) group. Hence, the factors which reduce the positive charge of the (C=O) group retard the reaction. In extreme cases, the reaction may not occur, e.g., *p*-dimethyl amino-benzaldehyde does not undergo Cannizzaro reaction.

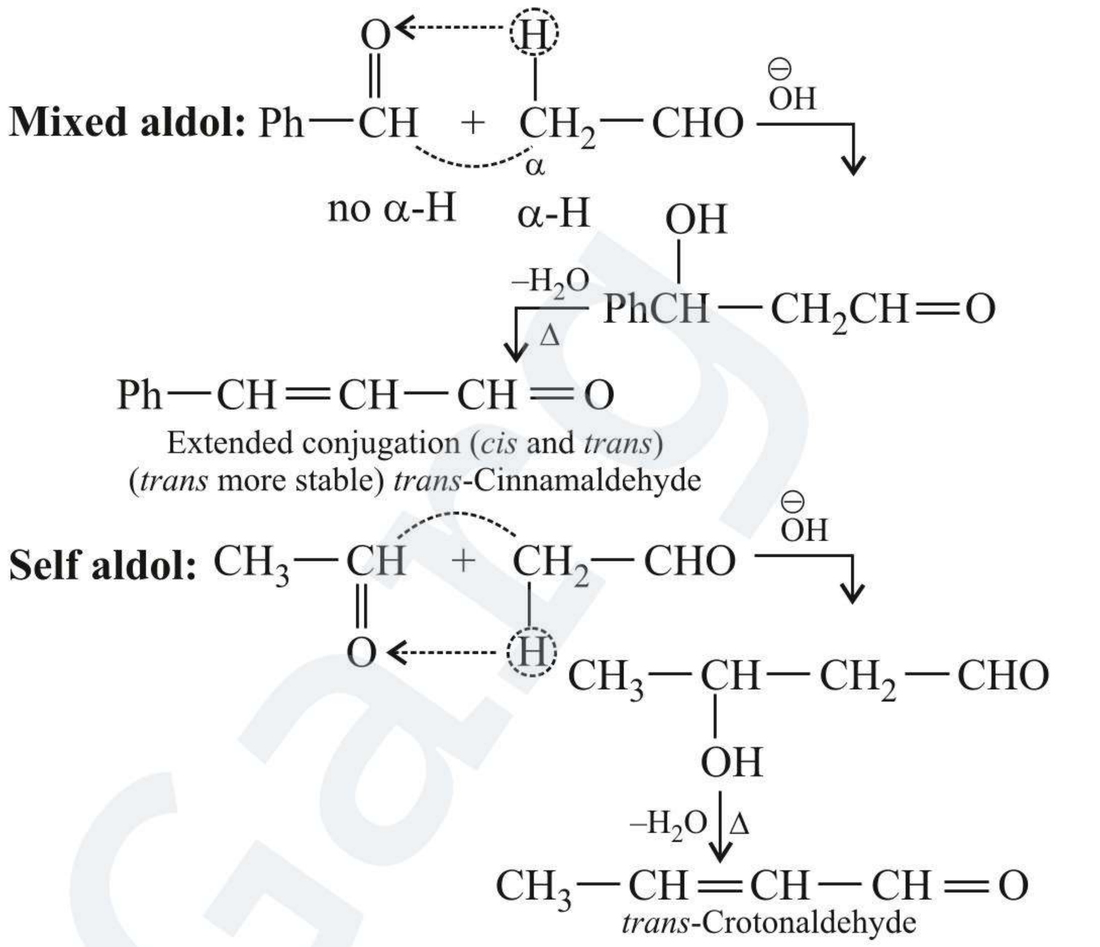


ii. Similarly, sterically hindered aldehydes do not undergo the reaction.

5.36 CLAISEN–SCHMIDT REACTION

Aldehydes lacking α-H atom in the presence of dilute base [aq. NaOH or (RONa in ROH)] condense with aldehydes or ketones containing α-H atom. It gives β-hydroxy carbonyl compound which undergoes rapid dehydration to give α,β- unsaturated carbonyl compounds. This reaction is called Claisen–Schmidt or simply Claisen reaction.

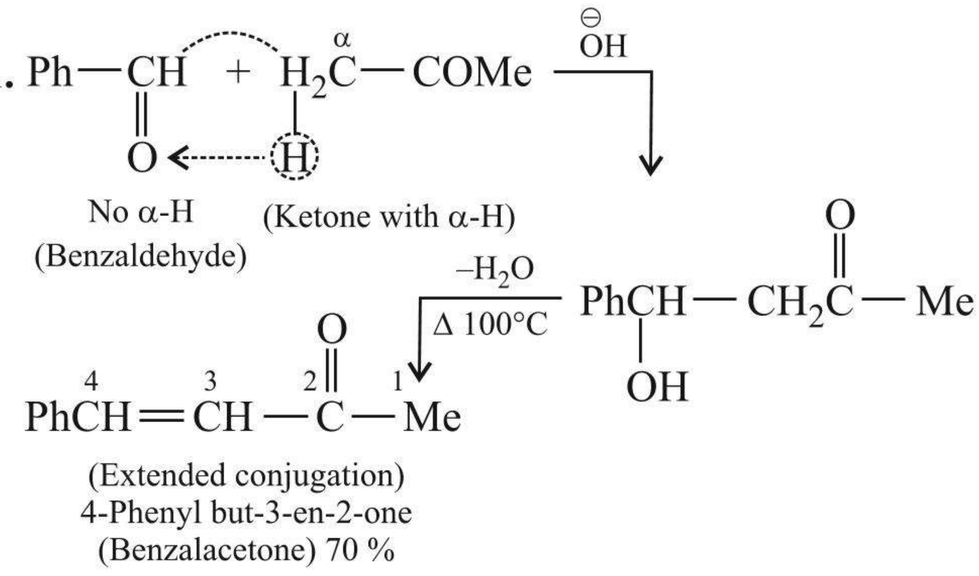
If one of the aldehydes has no α-H atom, it can only serve as an acceptor, thus eliminating two of the four possible aldol products.



i. Self aldol can be minimised by adding RCHO (with α-H) slowly to a large amount of PhCHO (with no α-H).

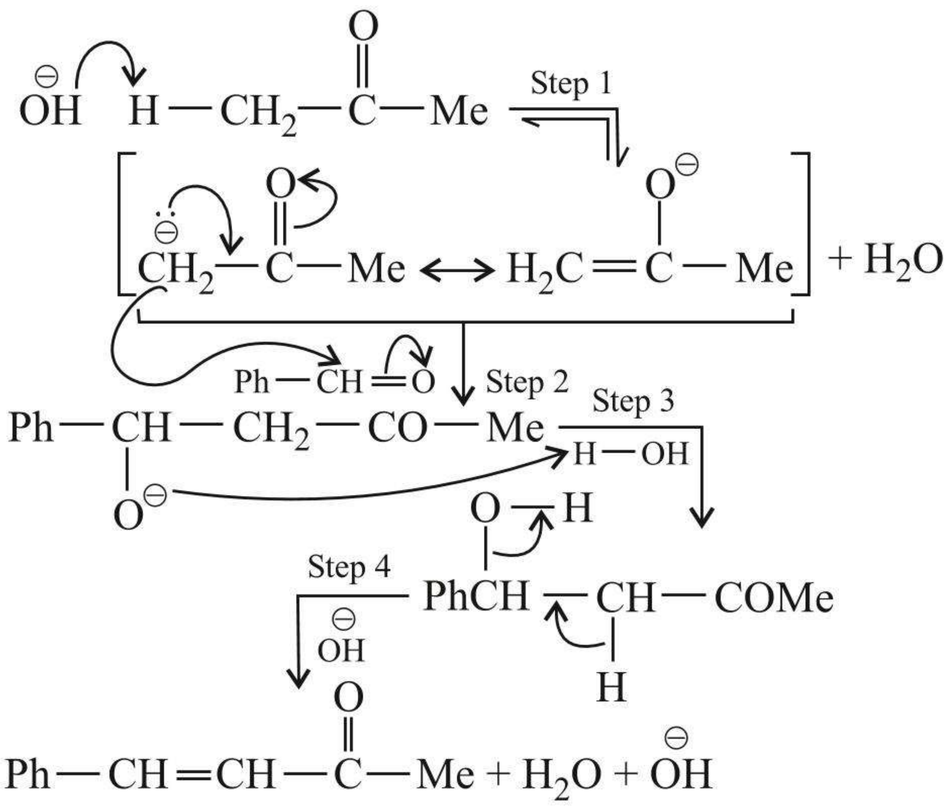
ii. Sometimes, Claisen–Schmidt reaction is also carried out using ketones as one of the components. Crossed aldol reactions are called Claisen–Schmidt reactions. Such reactions are practical when NaOH is used as the base. Under these conditions, ketones do not self condense appreciably because ketones are good carbanion (enolate anion) sources but poor acceptors. The equilibrium is unfavourable.

iii. Examples of Claisen–Schmidt reactions in which ketones do not undergo self aldol condensation, limiting to only one product:



5.36.1 Mechanism (Aldol Type)

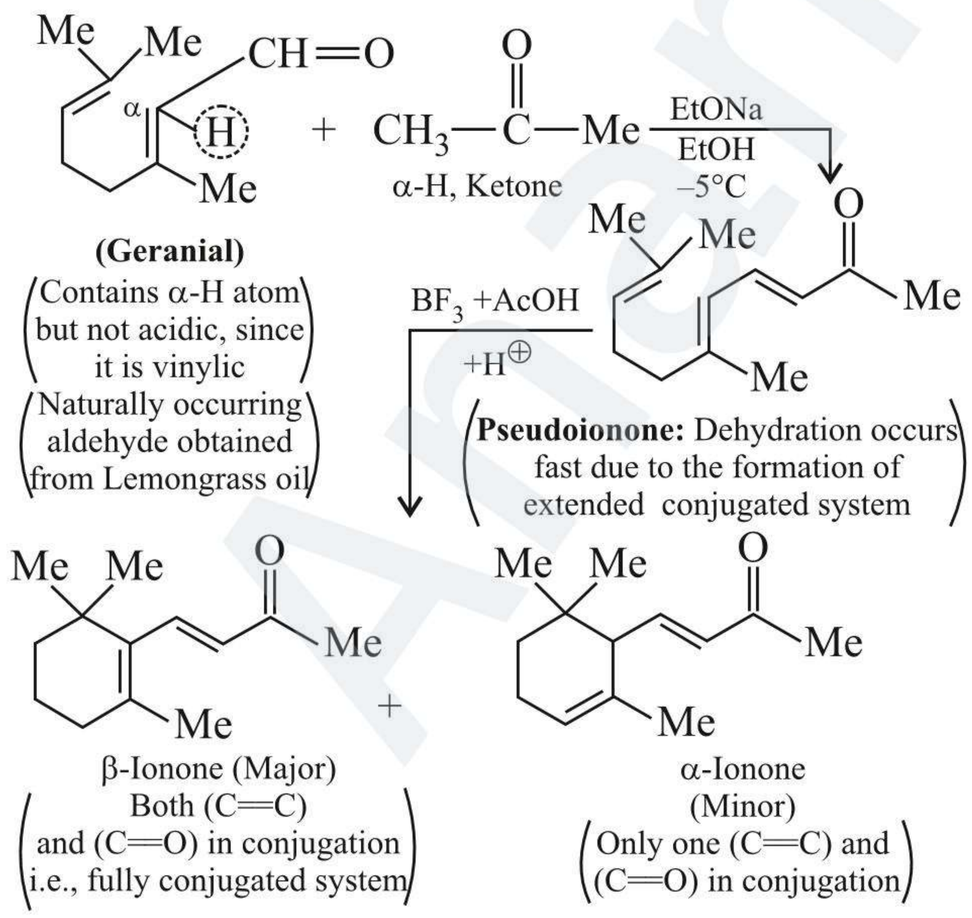
Base (NaOH) removes a proton from the α-C of ketone to give resonance-stabilised enolate anion (carbanion) which acts as a nucleophile and attacks the C atom of (C═O) of another molecule of aldehyde (with no H atom). It produces alkoxide anion, which removes an $H^{\oplus}$ ion from H_2O to give β-hydroxy ketone which on dehydration produces the α,β-unsaturated ketone (conjugated product).



In this reaction, dehydration occurs readily because the (C═C) bond that is formed conjugates with the (C═O) group and the benzene ring. The conjugated system is, therefore, extended.

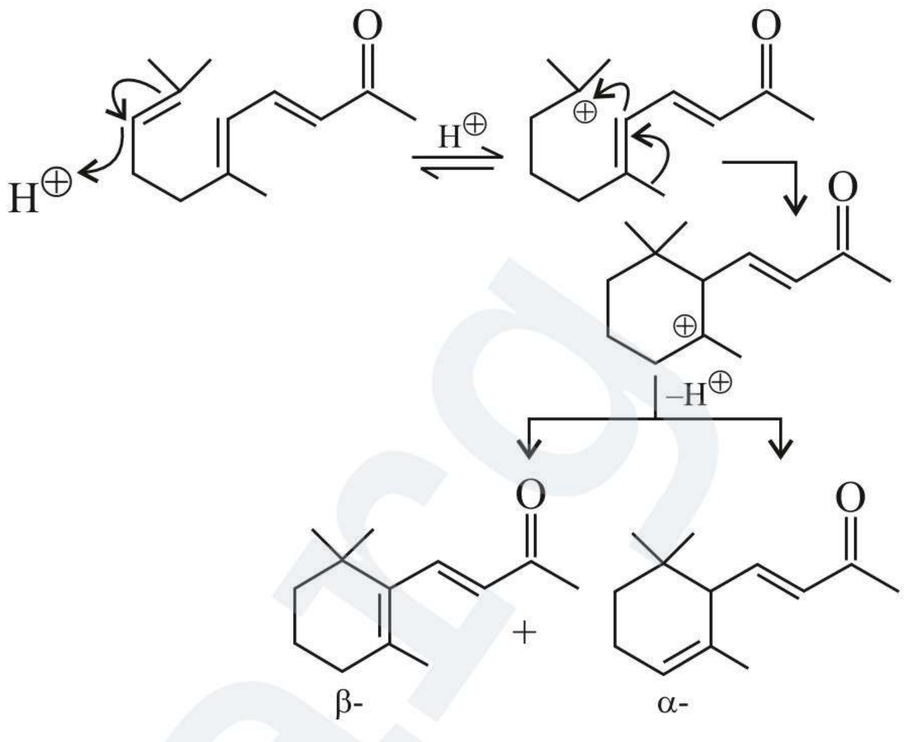
5.36.2 Application of Claisen–Schmidt Reaction

Synthesis of vitamin A precursor



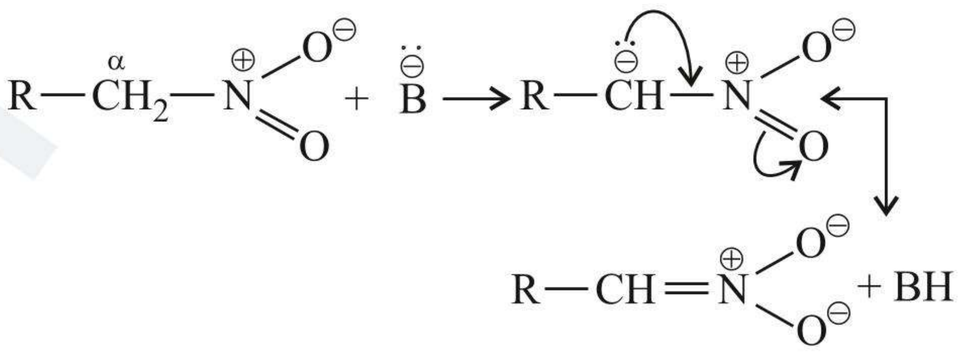
Vitamin A is synthesised from ionone.

5.36.3 Mechanism of Ring Closure

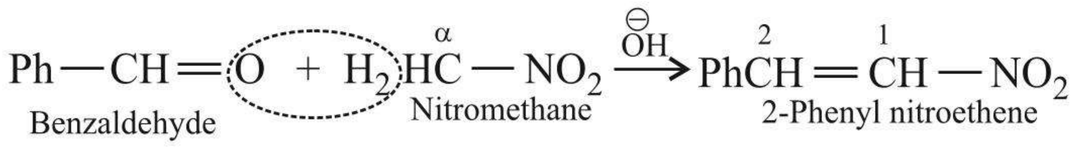


5.37 CONDENSATION WITH NITROALKANES

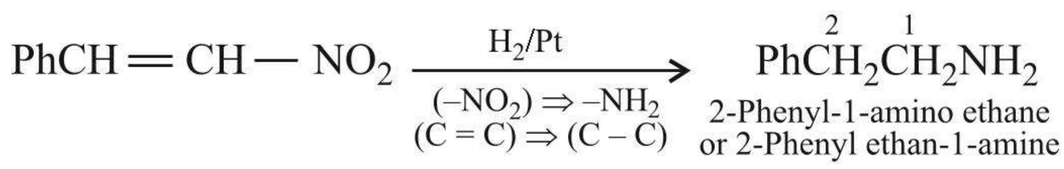
The α-H atoms of nitroalkanes are acidic (pK_a = 10), much more acidic than those of carbonyl compounds, due to $\bar{e}$- withdrawing effect of the ($-NO_2$) group and by the resonance stabilisation of the conjugate base anion.



Nitroalkanes with α-H atom undergo base-catalysed condensation with aldehydes and ketones that resemble aldol condensation, for example,



This condensation is useful because the nitro group of product can be easily reduced to an ($-NH_2$) group, e.g.,



5.38 CROSSED CANNIZZARO REACTION

When two different aldehydes lacking α-H atom are reacted in the presence of a strong base, they undergo disproportionation or redox reaction to give a molecule of alcohol and salt of an acid. Alcohol is obtained from the less reactive aldehyde and acid salt is obtained from the more reactive aldehyde.

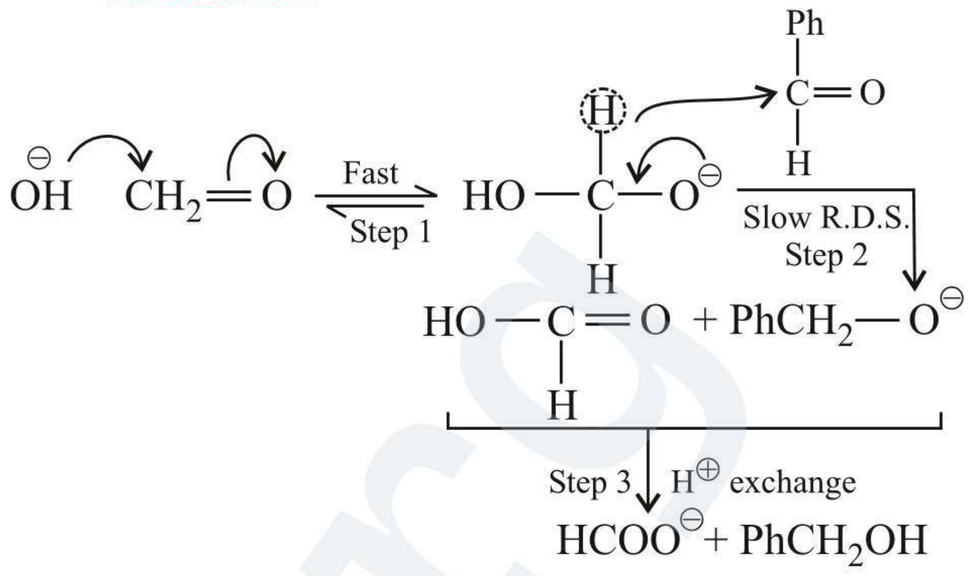
In Step 1 of the mechanism, $\overset{\ominus}{OH}$ attacks at the C of (C═O) group of more reactive aldehyde and gives adduct anion from which $H^{\ominus}$ ion is transferred to the less reactive aldehyde. It gives acid ion from more reactive aldehyde and alcohol from less reactive aldehyde, e.g.,

$$\underset{\text{(I) (More reactive than (II))}}{HCH{=}O} + \underset{\text{(II) (Less reactive than I)}}{PhCH{=}O} \xrightarrow{\overset{\ominus}{OH}} HCOO^{\ominus} + PhCH_2OH$$

($\overset{\ominus}{OH}$ attack at (I) and $H^{\ominus}$ transferred from adduct ion of (I))

$$\xrightarrow{\overset{\ominus}{OH}} CH_3OH + PhCOO^{\ominus}$$

5.38.1 Mechanism of Cross Cannizzaro Reaction



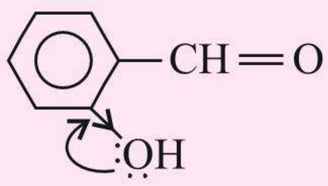
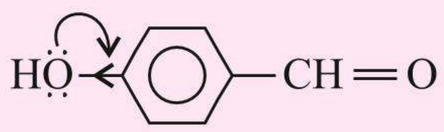
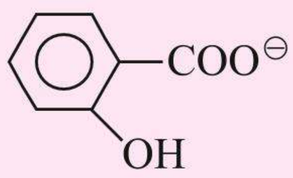
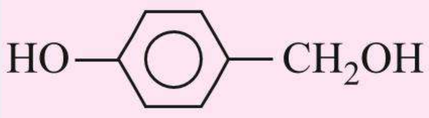
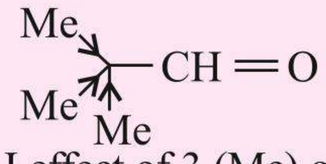
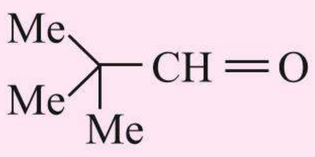
5.38.2 Reactivity Order in Crossed Cannizzaro Reaction

i. Aliphatic aldehydes are more reactive than aromatic aldehydes.

ii. Aldehydes containing $\bar{e}$ -withdrawing groups (–I or –R or both –I and –R) are more reactive than those containing $\bar{e}$ -donating groups (+I or +R, or both +I and +R) or with hyperconjugation (H.C.).

Table 5.5 List of some Crossed Cannizzaro's Product

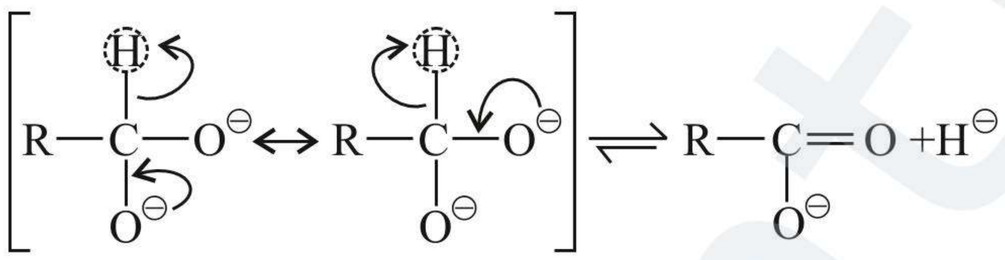
S.No.	More reactive aldehyde (I)	Less reactive aldehyde (II)	Crossed Cannizzaro products	
			Acid ion from (I)	Alcohol from (II)
1.	Ph — CH ═ O	Me → C6H4 — CH═O (+I and H.C. of Me)	$PhCOO^{\ominus}$	Me — C6H4 — CH_2OH
2.	Cl ← C6H4 — CH═O (–I effect of Cl)	Me → C6H4 — CH═O	Cl — C6H4 — $COO^{\ominus}$	Me — C6H4 — CH_2OH
3.	Cl ← C6H4 — CH═O	HÖ: ← C6H4 — CH═O (+R and –I of OH gp.)	Cl — C6H4 — $COO^{\ominus}$	HO — C6H4 — CH_2OH
4.	O_2N ← C6H4 — CH═O (–I and –R of NO_2)	Cl ← C6H4 — CH═O (–I of Cl)	O_2N — C6H4 — $COO^{\ominus}$	Cl — C6H4 — CH_2OH
5.	Me → C6H4 — CH═O (+I and H.C. of Me) (+I, $o > m > p$)	CH═O — C6H4 — Me (+I and H.C. of Me) But +I is greater at *ortho*	Me — C6H4 — $COO^{\ominus}$	CH_2OH — C6H4 — Me
6.	CH═O — C6H4 — Cl (–I effect is greater at *ortho* (–I, $o > m > p$)	CH═O — C6H4 — Cl (–I effect is slightly less at *m*)	$COO^{\ominus}$ — C6H4 — Cl	CH_2OH — C6H4 — Cl
7.	CH═O — C6H4 — Cl (–I effect is slightly greater at *m*- than *p*-	Cl ← C6H4 — CH═O	$COO^{\ominus}$ — C6H4 — Cl	Cl — C6H4 — CH_2OH

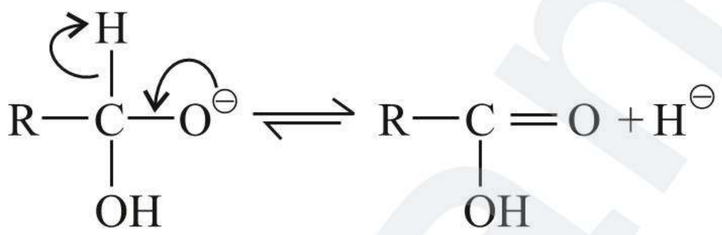
8.	 (+R effect is same at *o*- and *p*- position but –I at *o*- > *p*-; net $\bar{e}$-donating effect is less)	 Net $\bar{e}$-donating effect is slightly more		
9.	Ph←CH = O (– I and +R effect of Ph)	 (+I effect of 3 (Me) gps.)	$PhCOO^{\ominus}$	$Me_3C—CH_2OH$
10.	HCH=O		$HCOO^{\ominus}$	$Me_3C—CH_2OH$

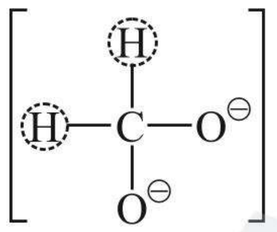
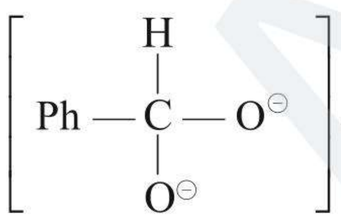
5.38.3 Best Hydride Ion Donor

When different intermediate adduct anions or adduct dianions are given, their hydride ion-donor capacity is determined by the charge density on the C atom of (C—H) bond from which $H^{\ominus}$ ion is ejected. Greater the negative charge density on the C of (C—H) group, greater is the tendency of $H^{\ominus}$ ion to leave the C atom.

i. Intermediate adduct dianion is a better $H^{\ominus}$ ion donor than the adduct anion. There is a statistical factor because dianion has two $O^{\ominus}$, so $\bar{e}$ migration from O atom occurs and $H^{\ominus}$ ion is lost easily.





ii.  (I) is a better hydride ion donor than  . Although both are dianions, but (I) is a better $H^{\ominus}$ ion donor (due to statistical factor) because (I) has two H atoms which can be lost as $H^{\ominus}$ ion.

iii. More the $\bar{e}$-donating groups (+I or +R or H.C. or all), more is the negative charge density on the C of (C—H) group, and as a result more easily the $H^{\ominus}$ ions are lost.

Decreasing order of $H^{\ominus}$ ion donor of the following:

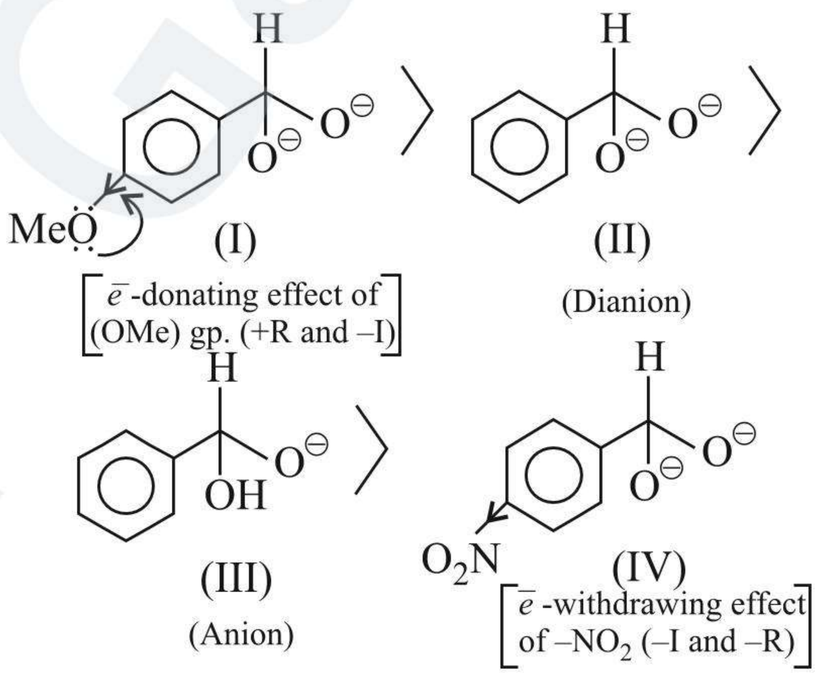
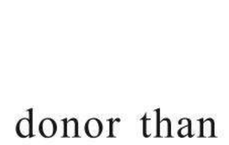


Illustration 5.15

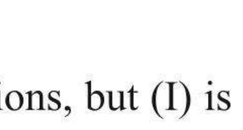
Give the decreasing order of $H^{\ominus}$ ion donor of the followings:

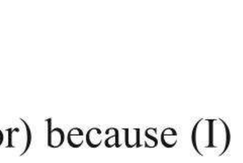
a. **I.** 

II.

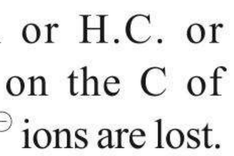
III. 

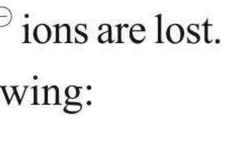
IV.

b. **I.** 

II. 

III.

IV. 

c. **I.** 

II. m—CH_3—C_6H_4—CH(—$O^{\ominus}$)—$O^{\ominus}$

III. p—CH_3—C_6H_4—CH(—$O^{\ominus}$)—$O^{\ominus}$

IV. C_6H_5—CH(—$O^{\ominus}$)—$O^{\ominus}$

Sol.

a. IV > III > II > I

More EWG, least is the $H^{\ominus}$ ion donor.

∴ IV (Standard) > III (–I of Cl at p-position) > II (–I of Cl at m–) > I(–I of Cl at o–)

[∵ –I power is: o – > m – > p– (+R is not considered)

b. IV > II > III > I

IV (Standard) > II (only –I of NO_2 at m–) > III (–I & –R of $–NO_2$ at p–) > I(–I & – of $–NO_2$ at o–]

[∵ –I & –R power of $–NO_2$ at o – > –I & –R power of $–NO_2$ at p–] [–R power of $–NO_2$ at o– & p– is same but –I power at o – > – I power at p–

c. I > III > II > IV

More EDG, best is the $H^{\ominus}$ ion donor.

+I power of $–CH_3$ group is: o – > p – > m –

[At o-position, +I & H.C. power $–CH_3$ group > +I & H.C. power of $–CH_3$ at p-position]

[H.C. power of $–CH_3$ at o- & p- positions are same but +I effect oif $–CH_3$ group at o-position > at p-position]

So decreasing order $H^{\ominus}$ ion donor is: **I > III > II > IV**.

5.38.4 Sterically Hindered Aldehydes Containing one α-H Atom

Isobutyraldehyde undergoes Cannizzaro reaction rather than aldol condensation.

$$2Me_3—\underset{\alpha}{\underset{|}{C}}(Me_2)—CH_1=O \xrightarrow[200°C]{NaOH}$$

(2-Methyl propan-1-al) or Isobutyraldehyde

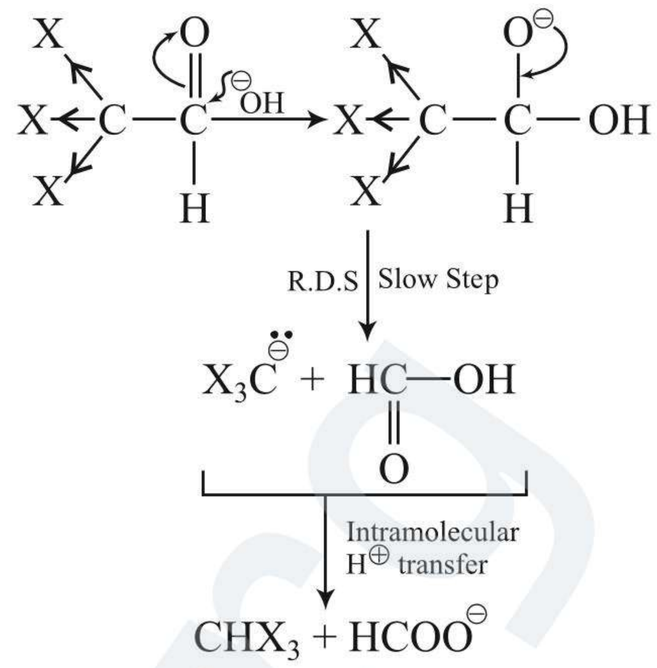
$$Me—CH(Me)—COO^{\ominus}Na^{\oplus} + Me—CH(Me)—CH_2OH$$

Sodium isobutyrate — Isobutyl alcohol

Isobutyraldehyde undergoes Cannizzaro reaction, although it contains one α-H atom because the mobility of α-H atom is arrested by the steric effect of two bulky methyl groups. and acidic character of H-atom is decreased due to +I effect of two Me-groups.

5.38.5 X_3C—CHO (X = F, Cl, Br, I) does not Undergo Cannizzaro Reaction

X_3C—CHO (X = F, Cl, Br and I) does not undergo Cannizzaro reaction.



Due to –I effect of three X-atoms, C—C bond is weaker than C—H bond. Thus $H^{\ominus}$ ion (hydride ion) transfer does not take place. Hence, it does not undergo Cannizzaro reaction.

5.38.6 When Different Moles of Two Different Aldehydes Undergo Crossed Cannizzaro and Cannizzaro Reactions

Two moles of HCHO and 1 mol of PhCHO react with conc. NaOH; quantitatively the products are:

i. Crossed Cannizzaro reaction:

$$\underset{1\text{ mol}}{HCHO} + \underset{1\text{ mol}}{PhCHO} \xrightarrow{\overset{\ominus}{O}H} \underset{1\text{ mol}}{HCOONa} + \underset{1\text{ mol}}{PhCH_2OH}$$

ii. Cannizzaro reaction:

$$\left[\begin{array}{l}\text{1 mol of HCHO left;}\\ \frac{1}{2}\text{ mol of HCHO react}\\ \text{with } \frac{1}{2}\text{ mol of HCHO}\end{array}\right]$$

$$\underset{\frac{1}{2}\text{ mol}}{HCHO} + \underset{\frac{1}{2}\text{ mol}}{HCHO} \xrightarrow{\overset{\ominus}{O}H} \underset{\frac{1}{2}\text{ mol}}{HCOONa} + \underset{\frac{1}{2}\text{ mol}}{CH_3OH}$$

Total moles of products = products (i) + products (ii)

$$\underset{1.5\text{ mol}}{HCOONa} + \underset{1\text{ mol}}{PhCH_2OH} + \underset{0.5\text{ mol}}{CH_3OH}$$

5.39 Internal Crossed and Intramolecular Cannizzaro Reaction

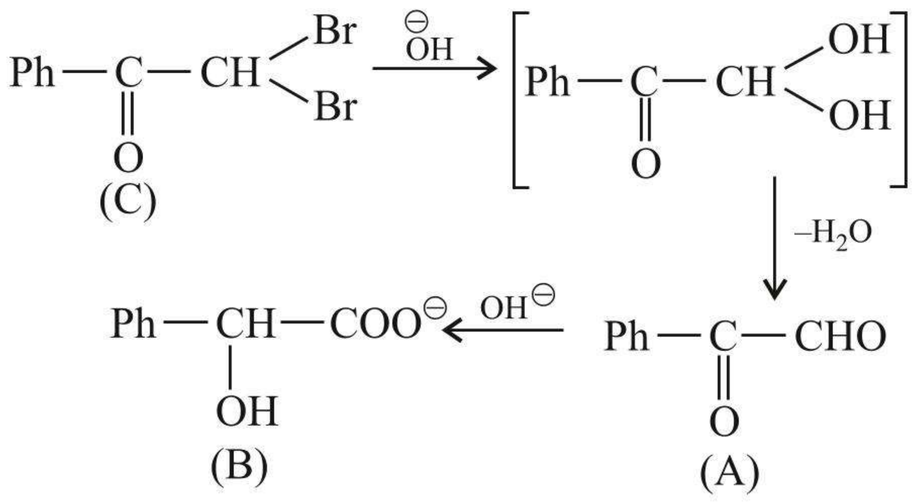
When a dialdehyde or a ketoaldehyde, lacking α-H atom, is reacted with a strong base, it undergoes internal crossed Cannizzaro reaction, e.g.,

i. Ph—C(=O)—CHO $\xrightarrow{\overset{\ominus}{O}H}$ Ph—CH(—OH)—$COO^{\ominus}$

(A) (Phenyl glycol) (no α-H atom) → (B)

The (—CHO) group is oxidised because it has the aldehydic H needed for $H^{\ominus}$ ion transfer. Keto group can only be reduced—not oxidised—in crossed Cannizzaro reactions.

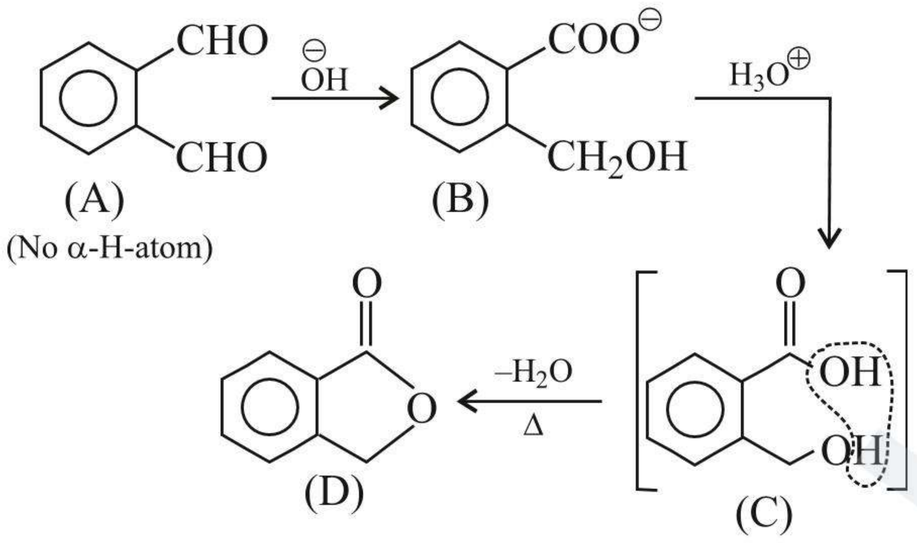
ii. a.



Compound (C) first undergoes alkaline hydrolysis to give compound (A) which with a strong base undergoes internal crossed Cannizzaro reaction to give (B).

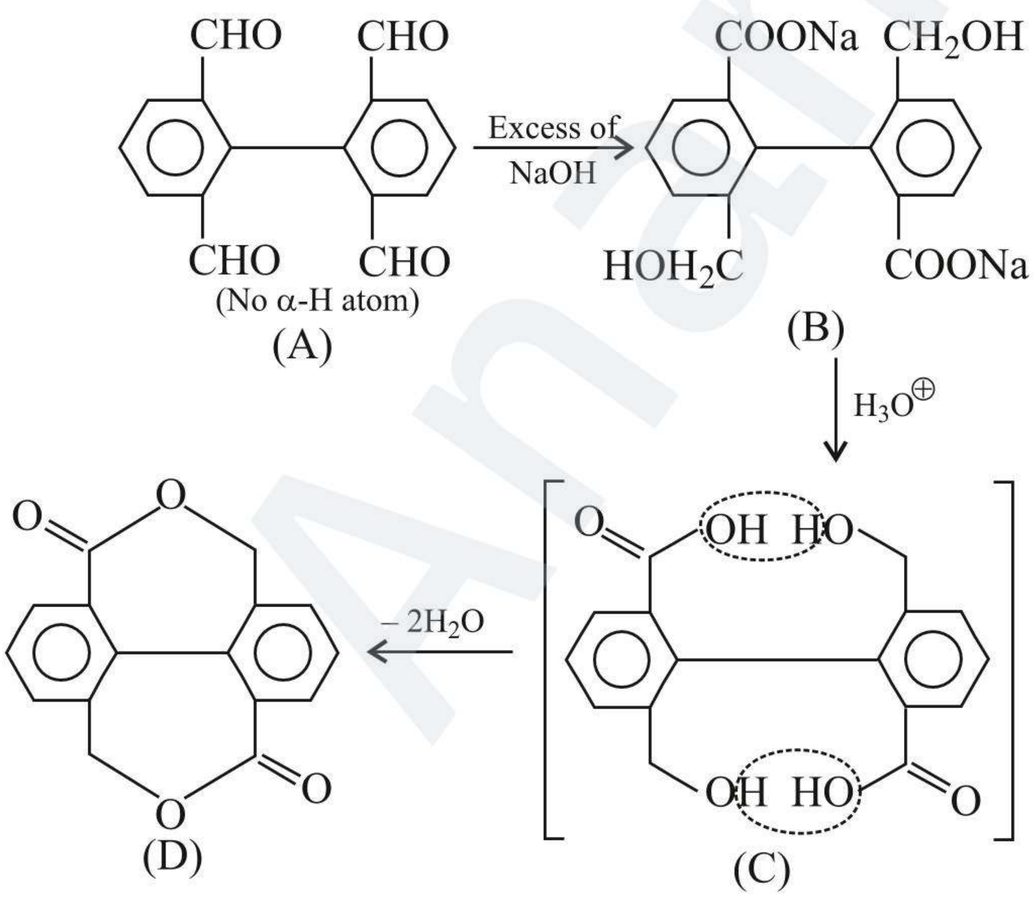
b. Similarly, $PhCX_2CHO$ and $PhCX_2CHX_2$ (X = Cl, Br, I) undergoes internal crossed cannizaro reaction with a strong base to give first (A) and then (B) above as in (a).

iii.



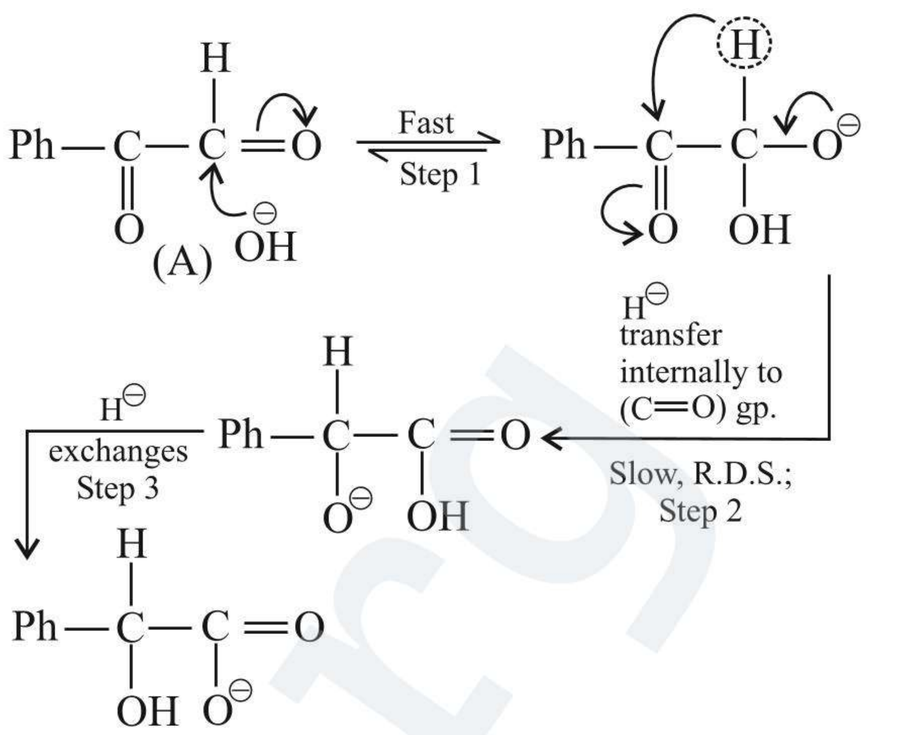
(A) is dialdehyde lacking α-H atom which undergoes internal crossed Cannizzaro reaction with a strong base to give (B). (B) on hydrolysis gives intermediate compound (C) containing free (—COOH) and (OH) groups, which react to form cyclic ester (D).

iv.



5.39.1 Mechanism

Proceed like Cannizzaro reaction:



i. When the concentration of strong base is low, rate = $K'[A]^2$ $[\overset{\ominus}{O}H]$; it is bimolecular with third-order kinetics, second-order w.r.t. compound (A), and first-order w.r.t. $OH^{\ominus}$ ion.

ii. When the concentration of strong base is high, mechanism proceeds like Cannizzaro reaction.

Rate = $K'[A]^2$ $[\overset{\ominus}{O}H]^2$

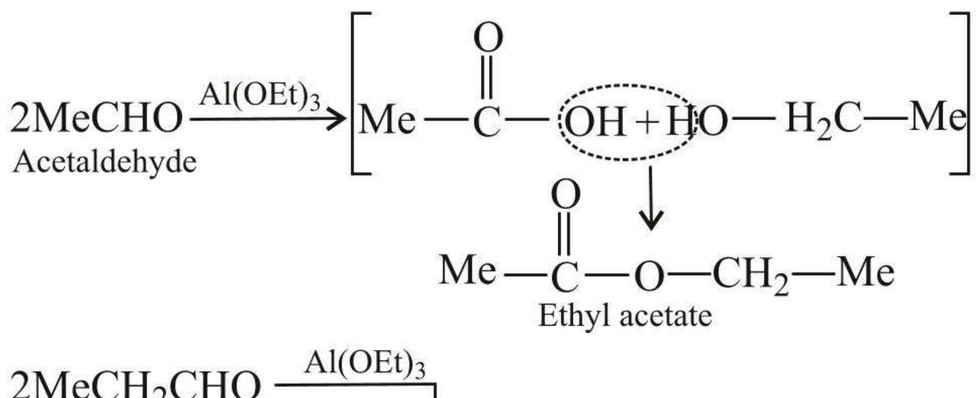
It is bimolecular with fourth-order kinetics, second- order w.r.t. compound (A), and second order w.r.t. $\overset{\ominus}{O}H$ ions.

5.40 TISHCHENKO REACTION

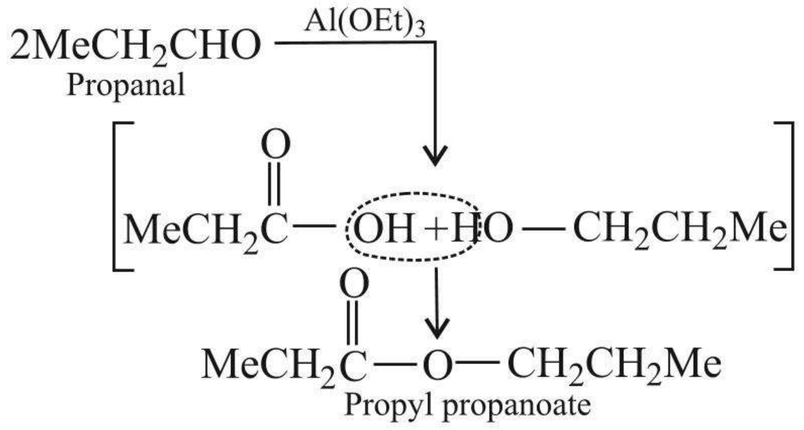
It is a modified form of Cannizzaro reaction and is also called Pseudo Cannizzaro reaction.

a. All aldehydes can be made to undergo Cannizzaro reaction with aluminium ethoxide, $Al(OEt)_3$, to give corresponding acid and alcohol. Under these conditions, the acid and alcohols are combined as the ester, e.g.,

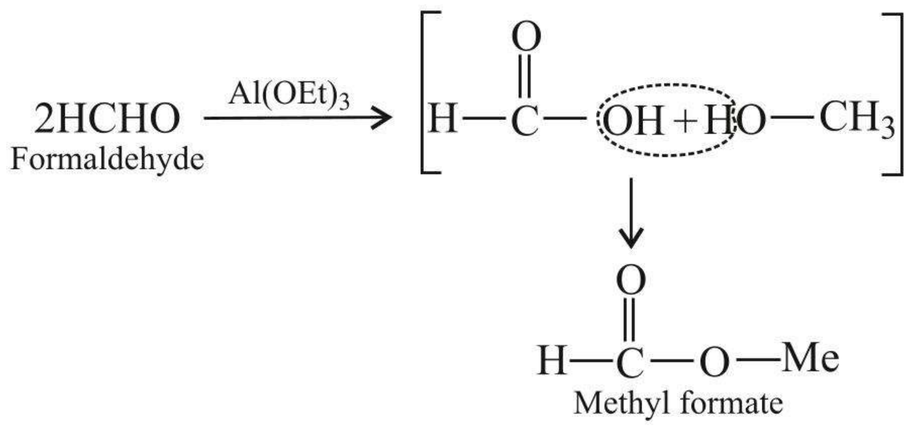
i.



ii.



iii.



5.40.1 Mechanism

The mechanism is uncertain, but there is a possibility involving an $H^{\ominus}$ ion shift as in the M.P.V. reduction.

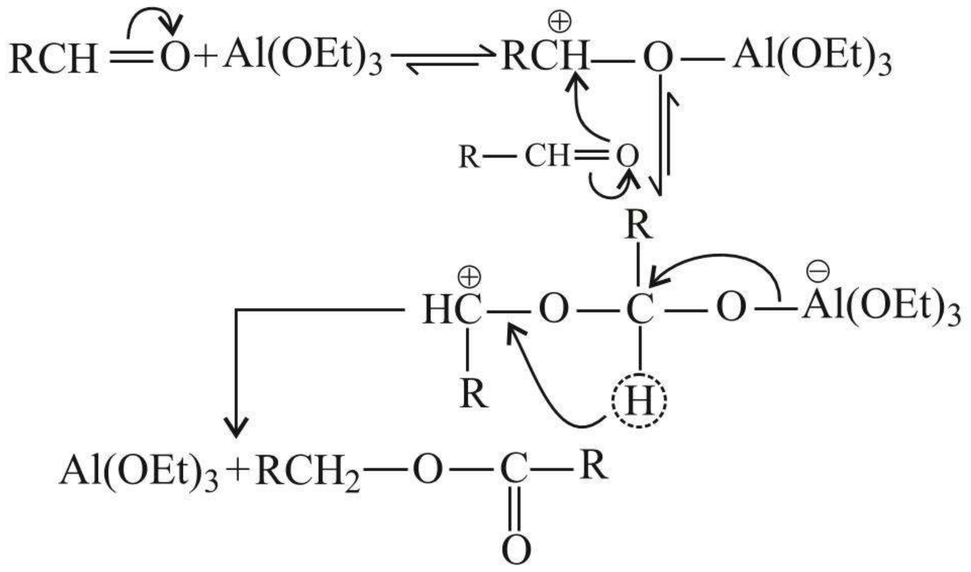


Illustration 5.16

Complete the following reactions:

a. Glyoxal (A) $\xrightarrow[2.\ H_3O^{\oplus}]{1.\ NaOH}$ (B)

b. Glyoxalic acid (A) $\xrightarrow[2.\ H_3O^{\oplus}]{1.\ NaOH/\Delta}$ (B) + (C)

c. CH_3CHO (A) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (B) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (C) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (D) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (E) + (F)

d. Me_2CHCHO (A) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (B) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (C) + (D)

e. $MeCH_2CHO$ (A) $\xrightarrow{2HCHO + \overset{\ominus}{O}H}$ (B) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (D) + (C)

Sol.

a. Glyoxal (A) $\xrightarrow[\text{Internal crossed Cannizzaro reaction}]{\overset{\ominus}{O}H}$ Sodium glycolate $\xrightarrow{H_3O^{\oplus}}$ (B) (Glycollic acid)

b. (A) + (A) $\xrightarrow[\text{Cannizzaro}]{\overset{\ominus}{O}H}$ Sodium glycolate + Disodium oxalate $\xrightarrow{H_3O^{\oplus}}$ Glycollic acid (B) + Oxalic acid (C)

c. (B) $\xrightarrow[\text{Claisen–Schmidt (C.S.R.)}]{HCHO + \overset{\ominus}{O}H}$ (Ist aldol) $\xrightarrow{HCHO + \overset{\ominus}{O}H}$ (2nd aldol) (C) Dihydroxymethyl acetaldehyde $\xrightarrow[\text{C.S.R.}]{HCHO + \overset{\ominus}{O}H}$ (3rd aldol) (D) (Trihydroxymethyl acetaldehyde) $\xrightarrow[\text{Crossed Cannizzaro reaction}]{HCHO + \overset{\ominus}{O}H}$ (4th aldol) (E) (Penta erythritol) + $HCOO^{\ominus}$ (F)

(Tetra methylol methane)

(E) is an important industrial product. Its ester with polybasic acids gives resin polymers used for surface coating. Its tetra nitro derivative (PETN) (penta erythritol tetra nitro) is a useful explosive.

d. (A) (Isobutyraldehyde) $\xrightarrow[\text{C.S.R.}]{\overset{\ominus}{O}H}$ (B) $\xrightarrow[\text{Crossed C.R.}]{HCHO + \overset{\ominus}{O}H}$ HCOONa (D) + (C)

e. (A) $\xrightarrow[\text{C.S.R.}]{2HCHO + \overset{\ominus}{O}H}$ (B) $\xrightarrow[\text{Crossed C.R.}]{HCHO + \overset{\ominus}{O}H}$ (D) + (C)

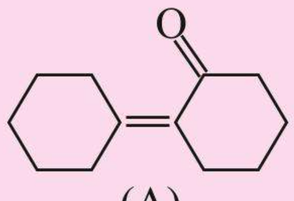
Illustration 5.17

Identify the products:

a. $PhCH{=}O + \text{cyclopentanone} \xrightarrow[(ii)\ H^{\oplus}]{(i)\ \overset{\ominus}{O}H}$ (A)

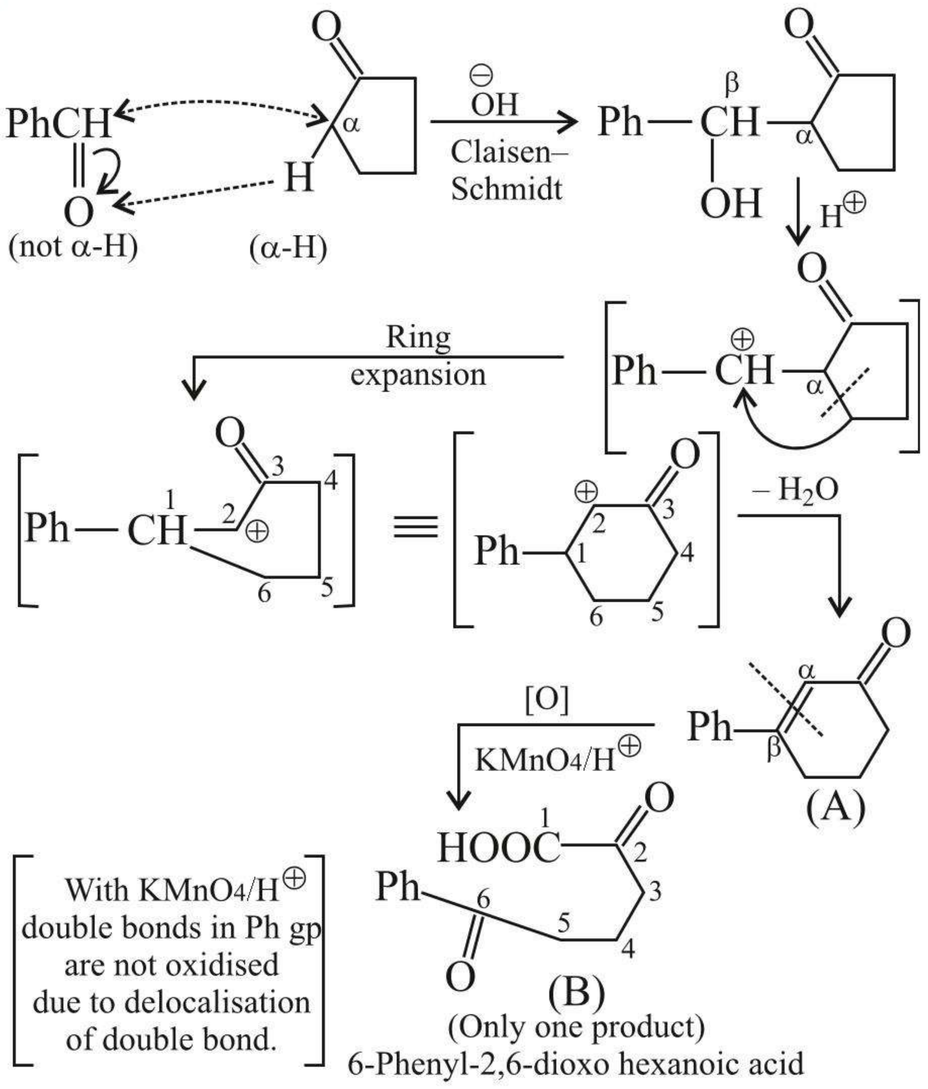
(A) $\xrightarrow{O_3/Red}$ (C) + (D) (Two products)

(A) $\xrightarrow{[O]\ KMnO_4/H^{\oplus}}$ (B) (Only one product)

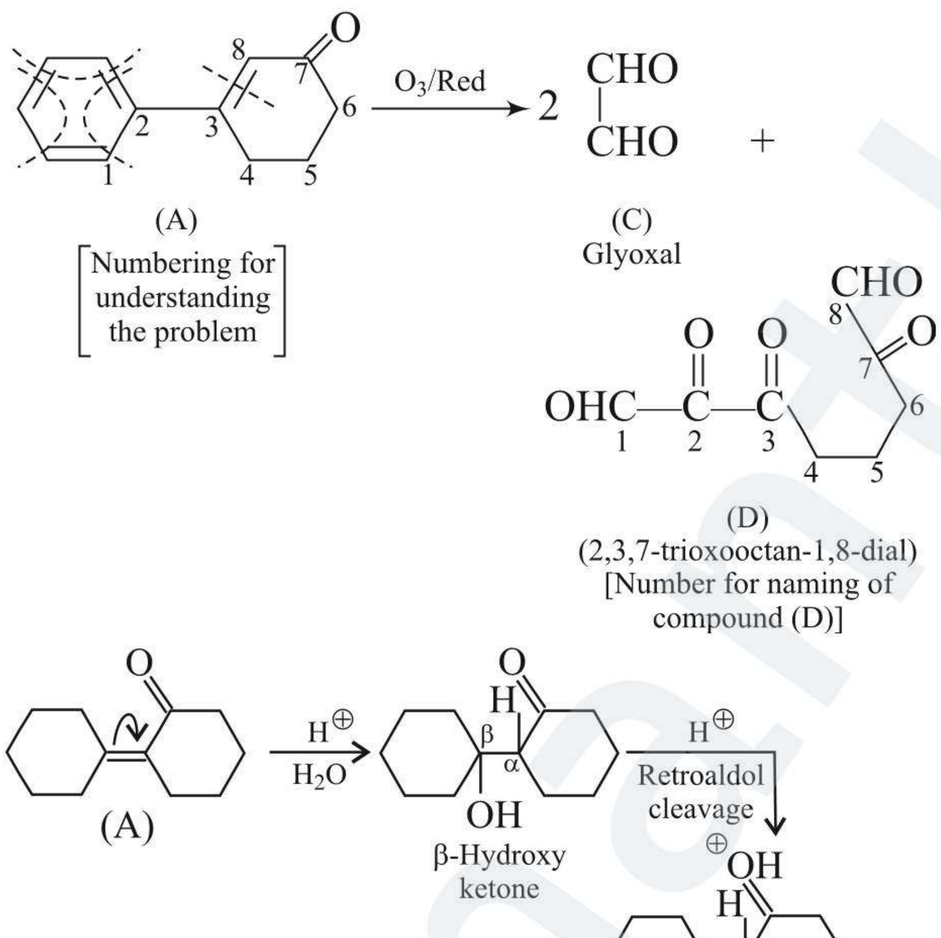
b.  (A) $\xrightarrow{\text{Aqueous acid}}$ (B) $(C_6H_{10}O)$ Forms an oxime $\xrightarrow{[O]}$ Adipic acid (C)

Sol.

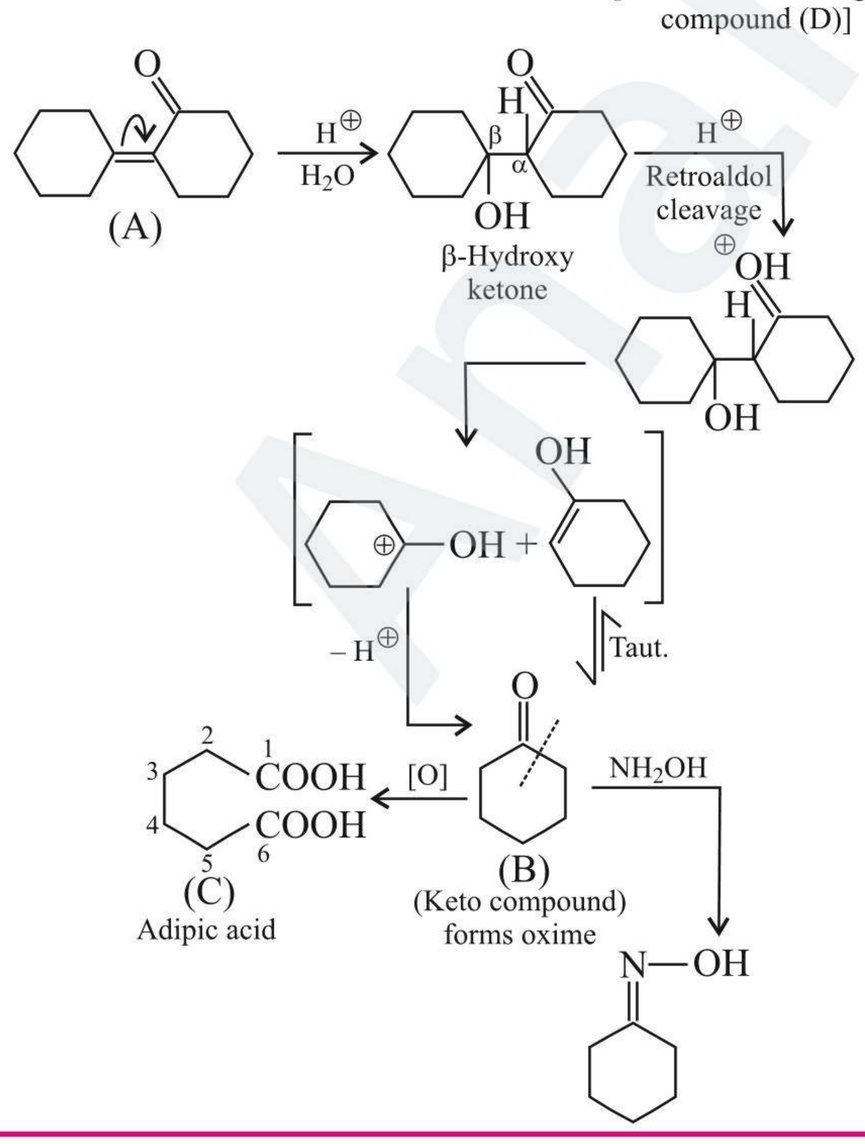
a. **i.**



ii. Product (A) is obtained as above in (i)



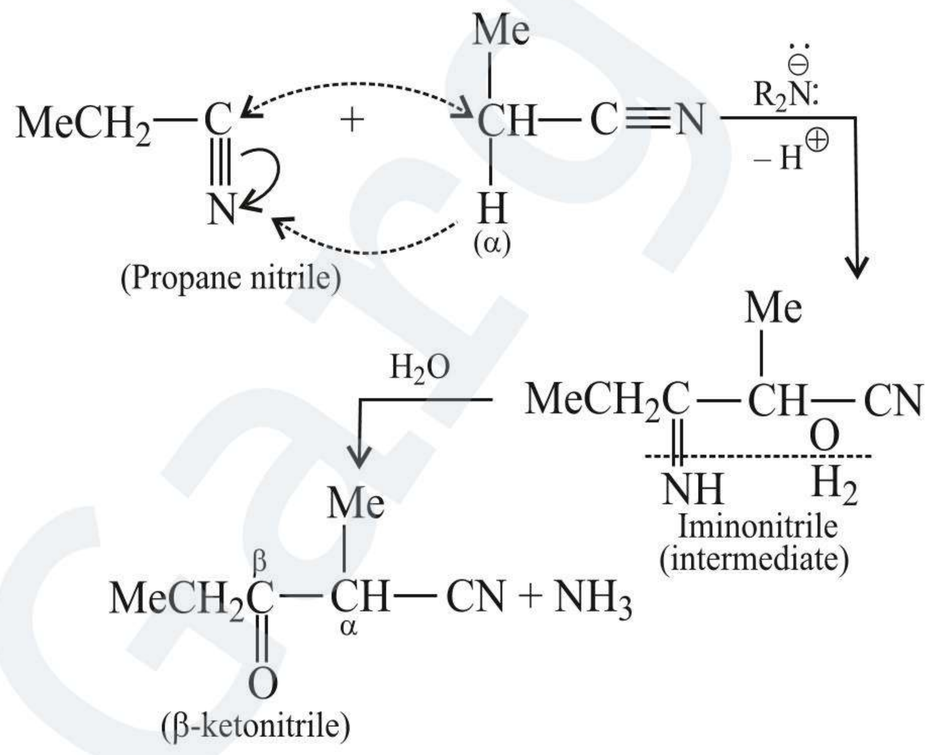
b.



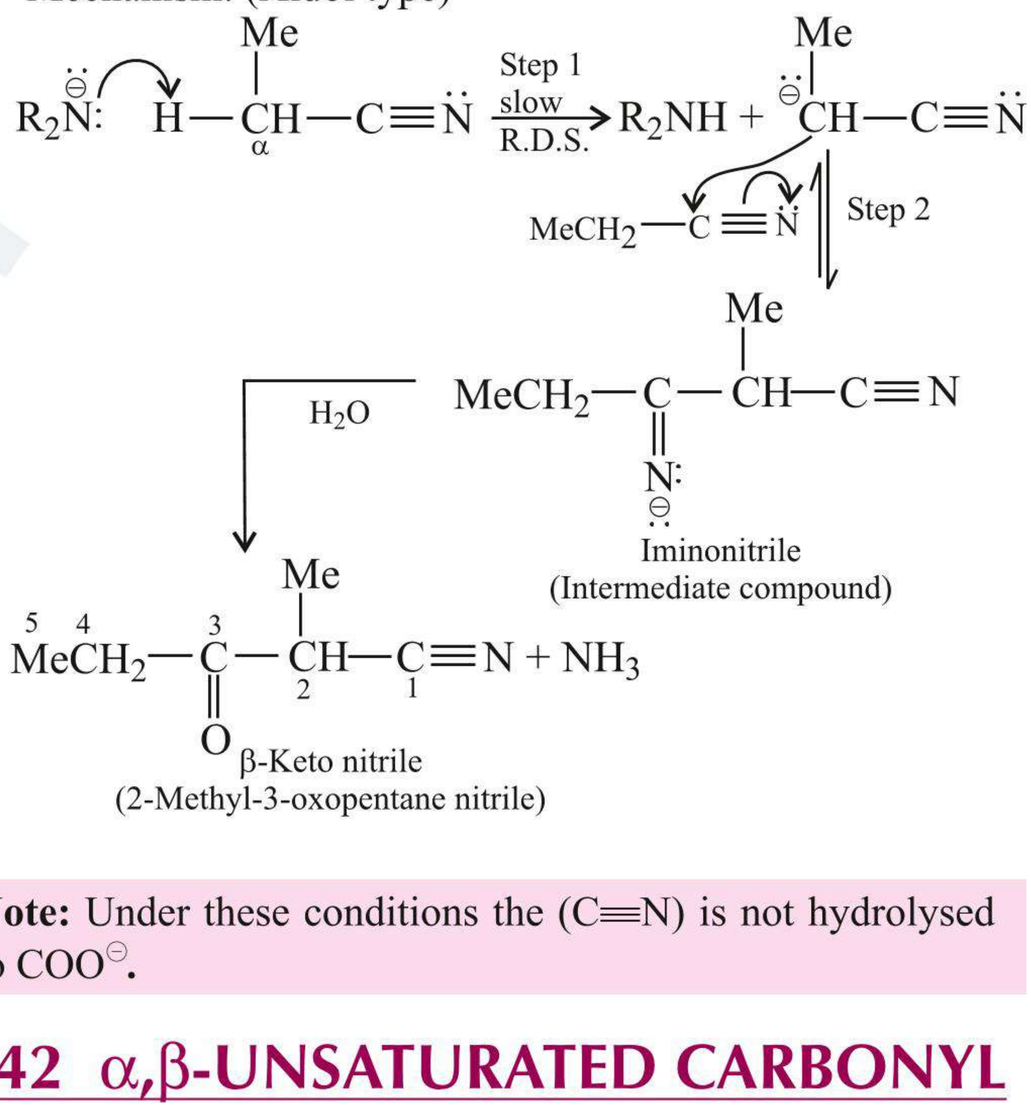
5.41 THORPE REACTION

Nitrile containing α-H atom in the presence of a base undergoes self condensation to give β-iminonitrile which on hydrolysis gives a β-keto nitrile. This reaction is called Thorpe reaction.

a. The nitrile is a carbanion source and (C ≡ N) acts as an acceptor, e.g.,



b. Mechanism: (Aldol type)



Note: Under these conditions the (C≡N) is not hydrolysed to $COO^{\ominus}$.

5.42 α,β-UNSATURATED CARBONYL COMPOUNDS (MICHAEL ADDITION)

Michael reaction: The addition of active methylene group (addenda) of (C═C) of α,β-unsaturated compounds (acceptors) in the presence of NaOEt or piperidine is called Michael reaction. All α,β-unsaturated compounds possessing a nitrile or a carbonyl group in conjugation with (C═C) are acceptors.

PhCH═CHCOPh (Chalcones); PhCH═CHOOEt (Cinnamates).

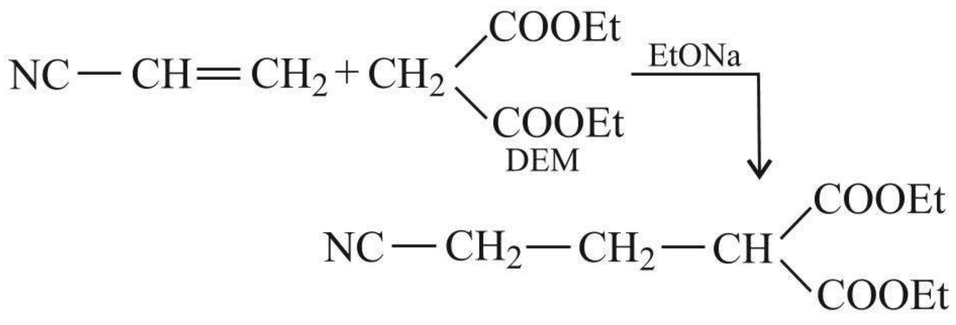
Me_2C═CHCOCH$_3$ (Mesityl oxide); CH_2═CHCOOEt (Acrylic ester).

$EtOOC—CH=CH—COOEt$ (Fumaric ester); $CH_2=CHCN$ (Nitriles); $CH_2=CH—CHO$ (Aldehydes)

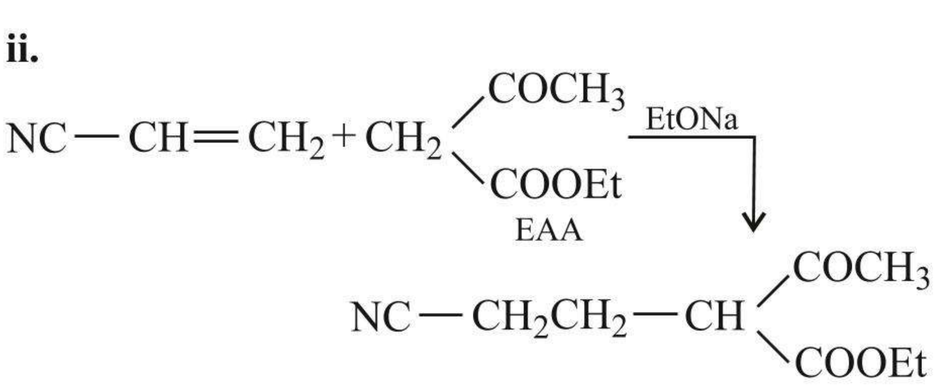
The (C=C) must be bonded to a functional group capable of stabilising the negative charge.

Addenda ⇒ Malonic ester, EAA, cyanoacetic ester, phenyl acetic esters, aliphatic nitro compounds, benzyl cyanide.

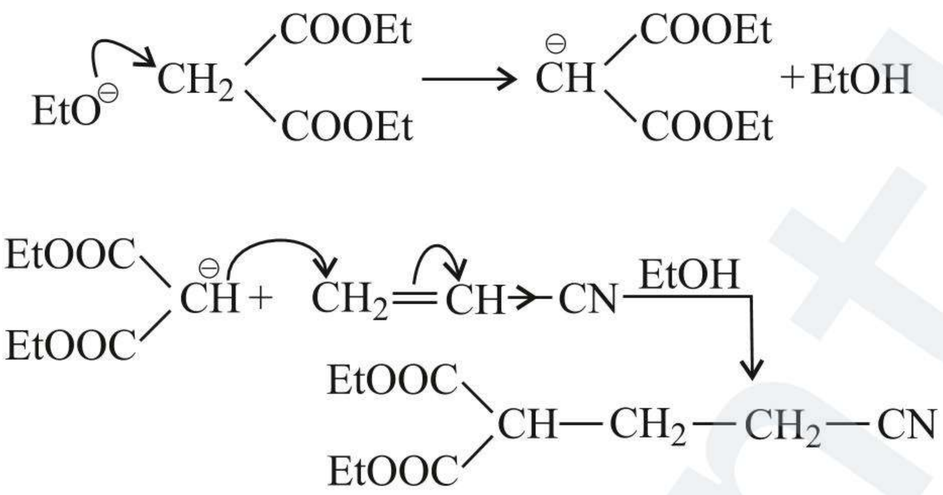
i.



ii.

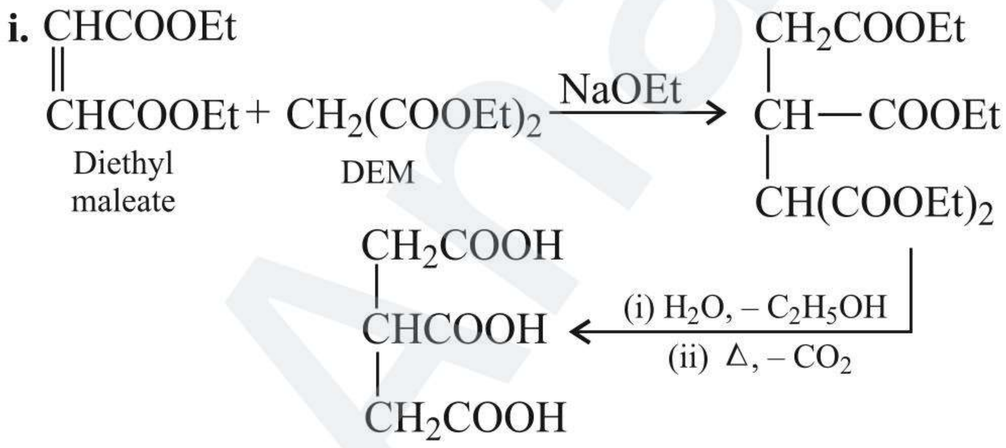


5.42.1 Mechanism

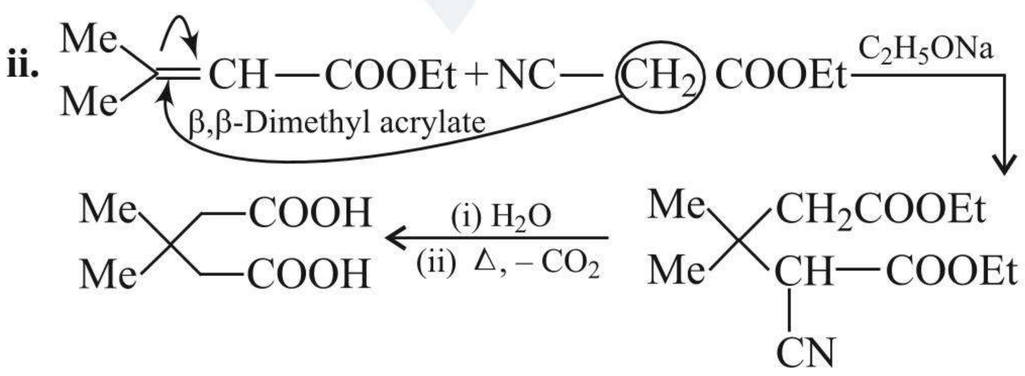


5.42.2 Examples

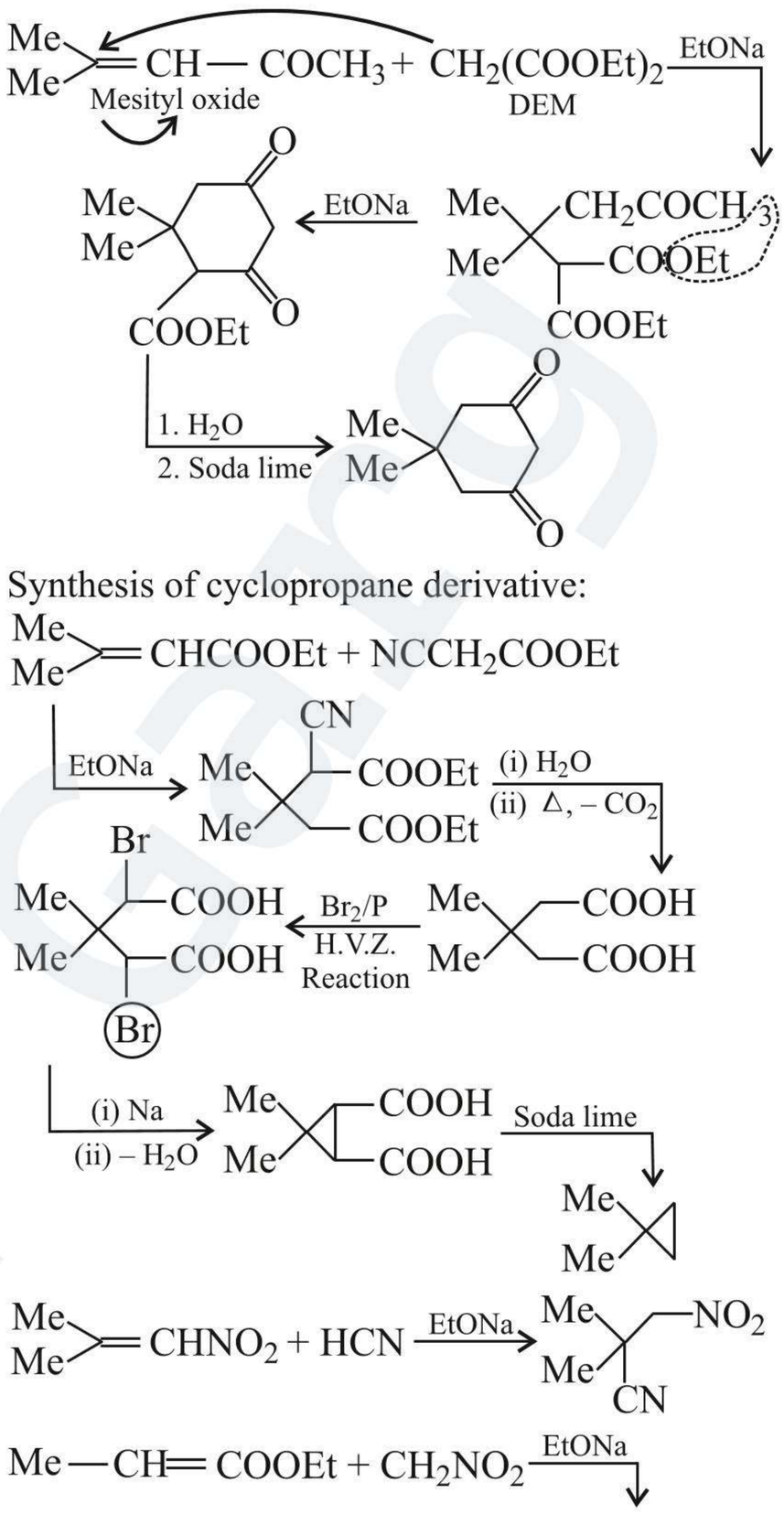
i.



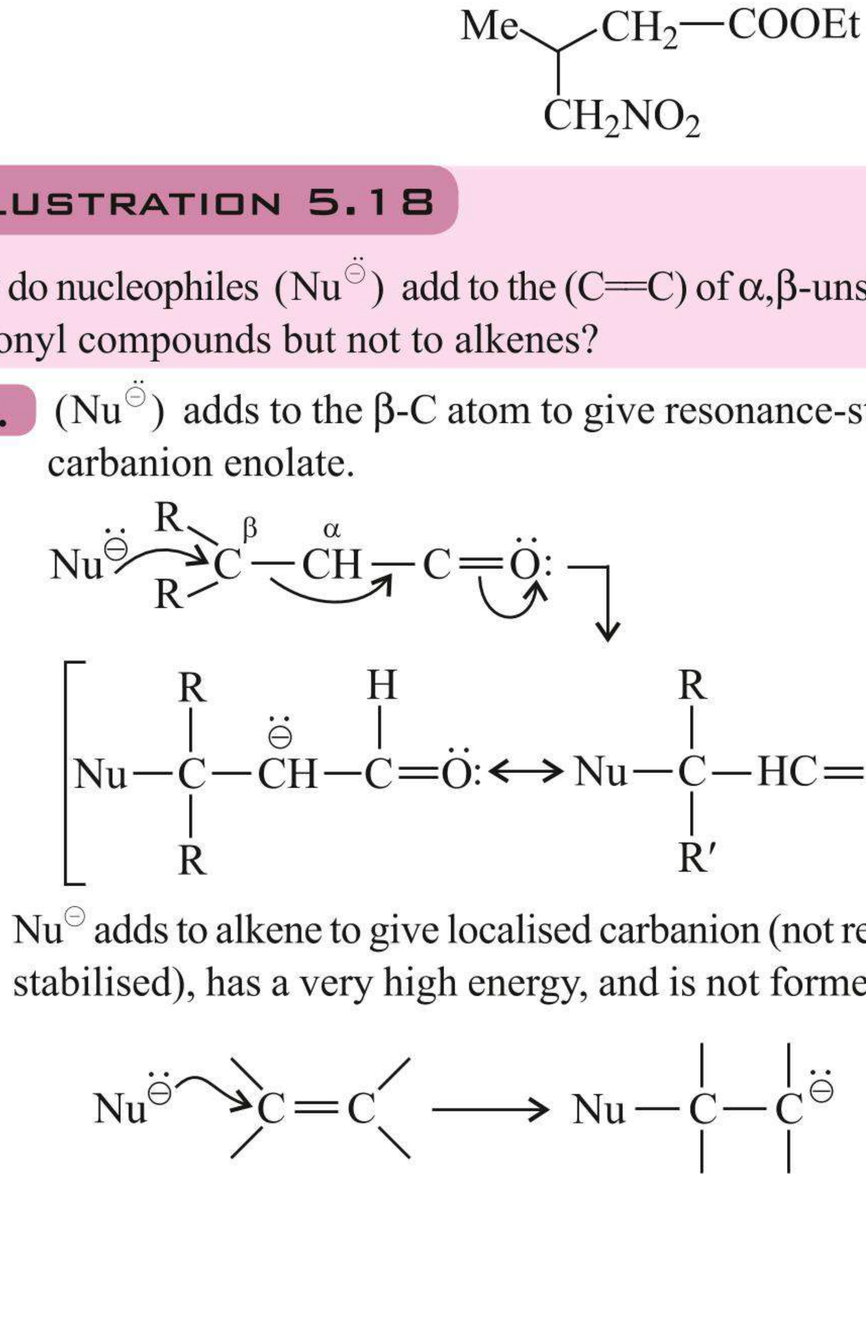
ii.



iii. Synthesis of dimedone:



iv. Synthesis of cyclopropane derivative:



v.

vi.

Illustration 5.18

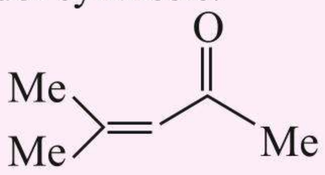
Why do nucleophiles ($Nu^{\ominus}$) add to the (C=C) of α,β-unsaturated carbonyl compounds but not to alkenes?

Sol. ($Nu^{\ominus}$) adds to the β-C atom to give resonance-stabilised carbanion enolate.

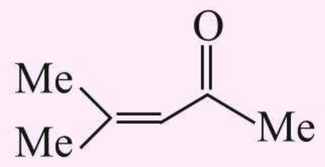
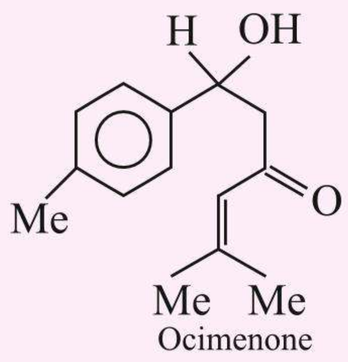
$Nu^{\ominus}$ adds to alkene to give localised carbanion (not resonance stabilised), has a very high energy, and is not formed easily.

Concept Application Exercise 5.2

1. Complete the missing reactant in the following directed aldol synthesis.

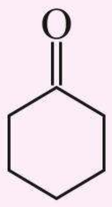
a.  + (B) $\xrightarrow{\text{Directed aldol reaction}}$ 

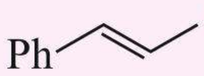
α-Bisabolanone
(C)

b.  + (B) $\xrightarrow{\text{Directed aldol reaction}}$ 

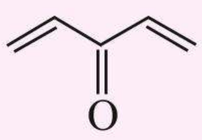
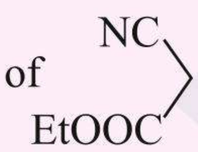
Ocimenone
(C)

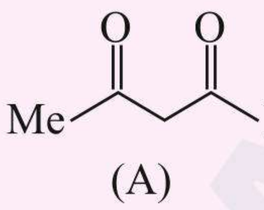
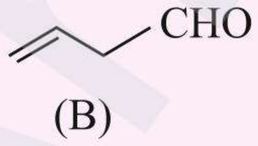
2. Complete the following reactions:

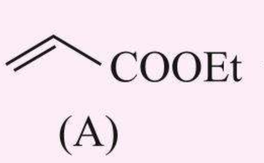
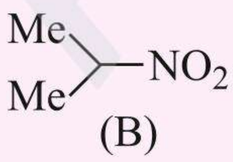
a.  (A) +  (B) $\xrightarrow{\ominus OH}$ (C) $\xrightarrow{H_2O}$ (D)

b. AAE +  (B) $\xrightarrow{NaOEt}$ (C) $\xrightarrow{H_2O}$ (D)

(A)

c.  (A) + 2 eq. of  (B) $\xrightarrow{NaOEt}$ (C) $\xrightarrow{H_2O}$ (D)

d.  (A) +  (B) $\xrightarrow{NaOEt}$ (C) $\xrightarrow{H_2O}$ (D)

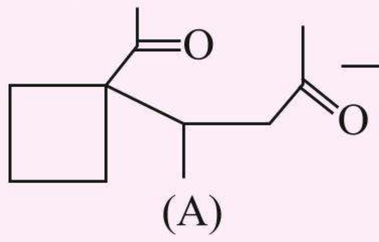
e.  (A) +  (B) $\xrightarrow{\ominus OH}$ (C) $\xrightarrow{H_2O}$ (D)

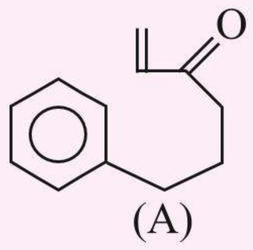
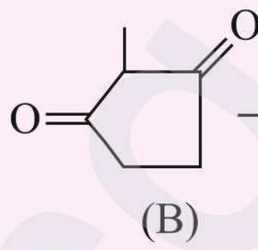
f. AAE +  (B) $\xrightarrow{NaOEt}$ (C) $\xrightarrow{H_2O}$ (D)

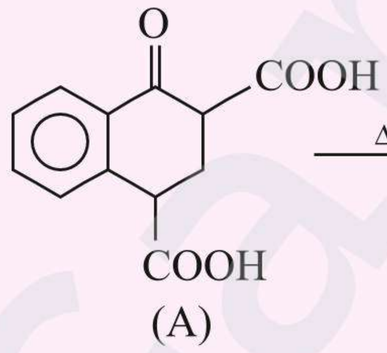
(A)

g.  (A) + HBr (B) $\longrightarrow$ (C) + (D)

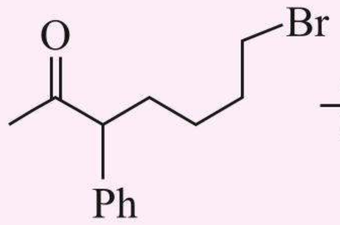
3. Identify the reactants/products:

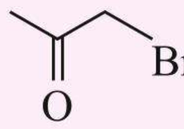
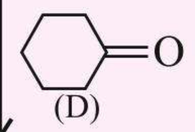
a.  (A) $\xrightarrow{\ominus OH}$ (B)

b.  (A) +  (B) $\xrightarrow{\ominus OH,\Delta}$ (C)

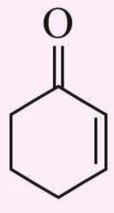
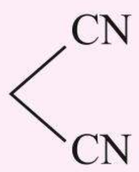
c.  (A) $\xrightarrow{\Delta}$ (B) $\xrightarrow[\text{or } Br_2/CH_3COOH]{Br_2/\text{Red P}}$ (C) $\xrightarrow[KOH]{\text{alc.}}$ (D)

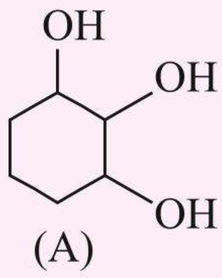
d.  (A) $\xrightarrow{Br_2/CH_3COOH}$ (B) $\xrightarrow[DMF]{Li_2CO_3,\Delta}$ (C)

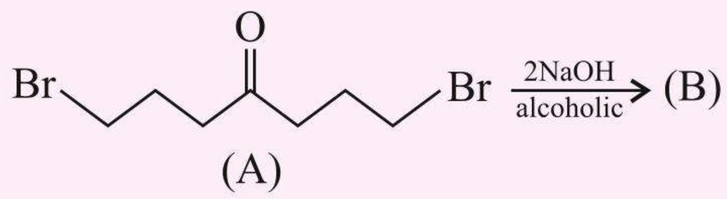
e.  (A) $\xrightarrow[DMSO]{C_2H_5O^{\ominus}}$ (B) (Major)

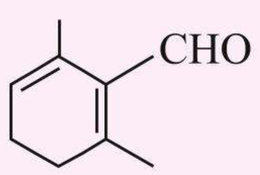
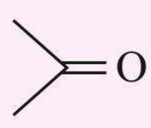
f.  (A) + Ph_3P (B) $\xrightarrow[ether]{CH_3Li}$ (C) $\longrightarrow$  (D)

(E)

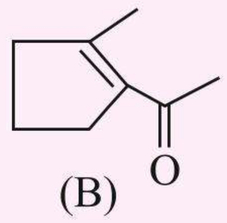
g.  (A) +  (B) $\xrightarrow[EtOH]{EtO^{\ominus}}$ (C) $\xrightarrow[②\text{Sodalime}]{①\ H_3O^{\oplus}}$ (D)

h.  (A) $\xrightarrow[H^{\oplus}]{EtOH}$ (B)

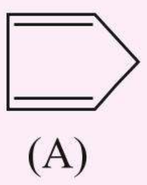
i.  (A) $\xrightarrow[\text{alcoholic}]{2NaOH}$ (B)

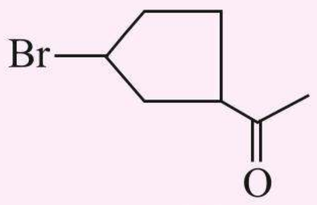
j.  (A) +  (B) $\xrightarrow{EtO^{\ominus}/EtOH}$ (C)

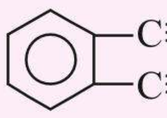
k. (A) $\xrightarrow{\ominus OH}$ (B)



l. (A) + (B) $\xrightarrow[\Delta]{EtO^{\ominus}}$ (C) $\xrightarrow{O_3/Red}$ (D) + (E)



m.  (A) $\xrightarrow[H_2SO_4]{MeOH(excess)}$ (B) $\xrightarrow[(ii)\ \text{O}]{(i)\ Mg/ether}$ C $\xrightarrow{H_3O^{\oplus}}$ (D)

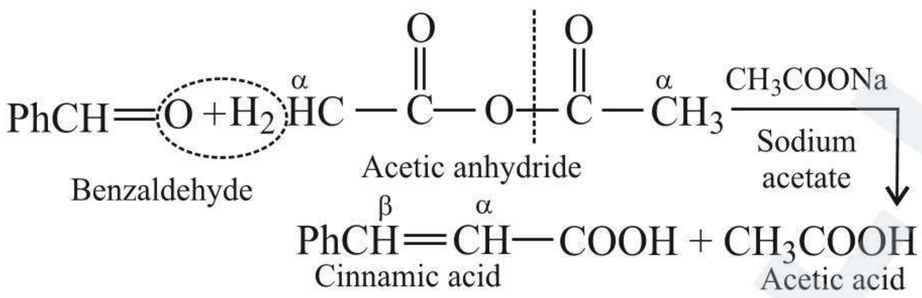
n.  $\xrightarrow[H_2SO_4]{Hg^{2+}}$ (B) $\xrightarrow[\Delta]{Dil\ NaOH}$ (C) $\xrightarrow[H_3O^{\oplus}]{Ph\ Mg\ Br}$ (D)

5.43 PERKIN REACTION

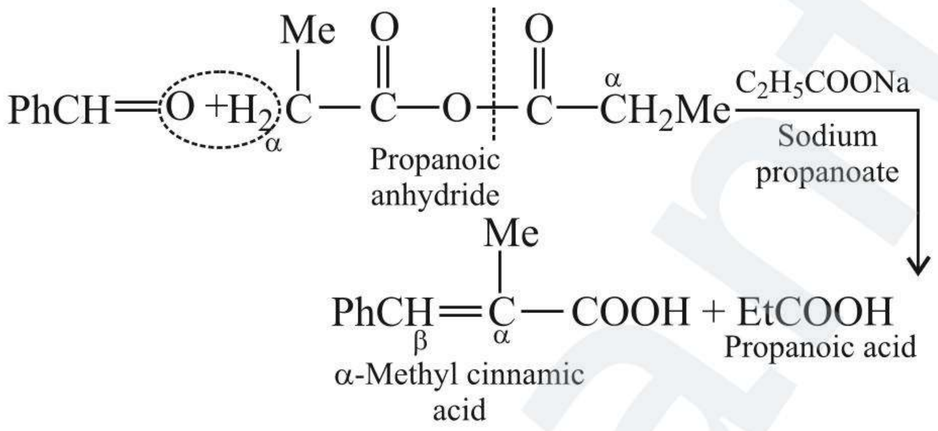
a. Aromatic aldehydes when heated with the anhydride of an aliphatic acid (containing two α-H atoms) in the presence of its sodium or potassium salt result in condensation to form α,β-unsaturated acid.

Reactivity of substituted aldehydes at *p*-position: NO_2 > Cl > H > R > OR.

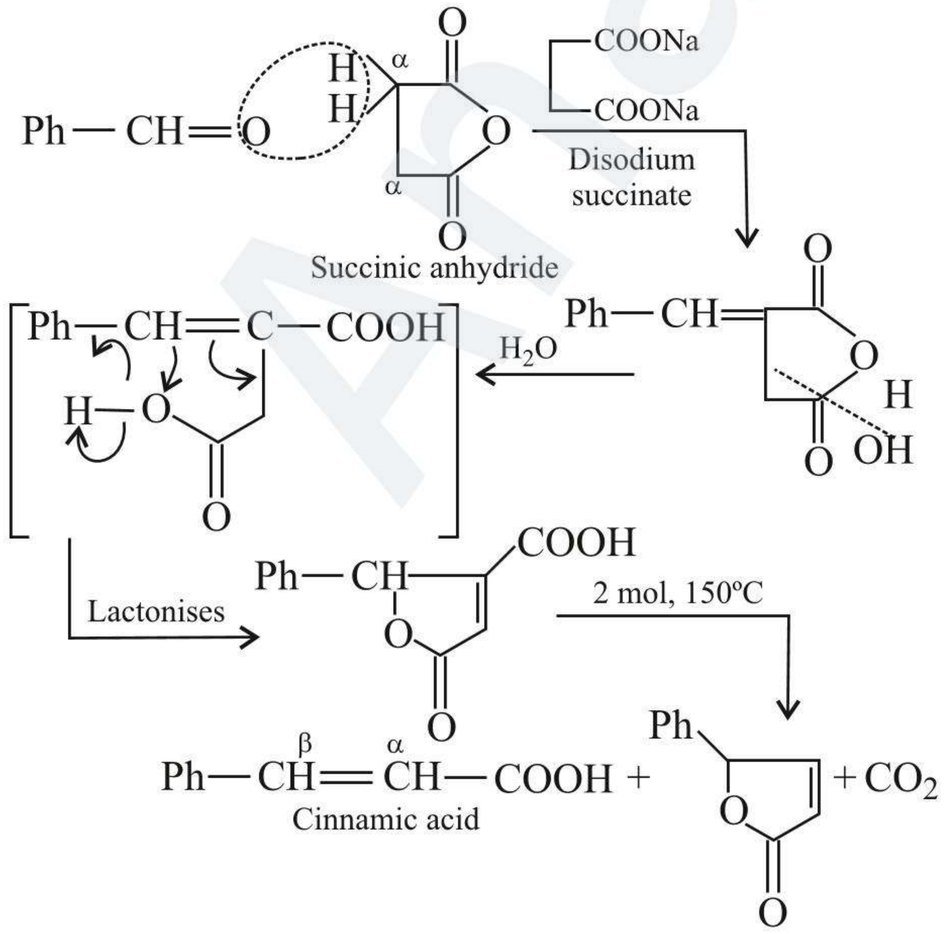
i.



ii.

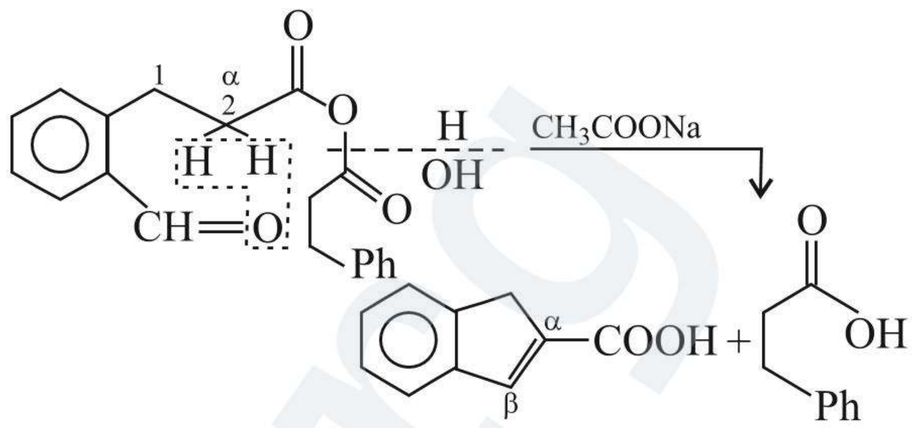


iii.

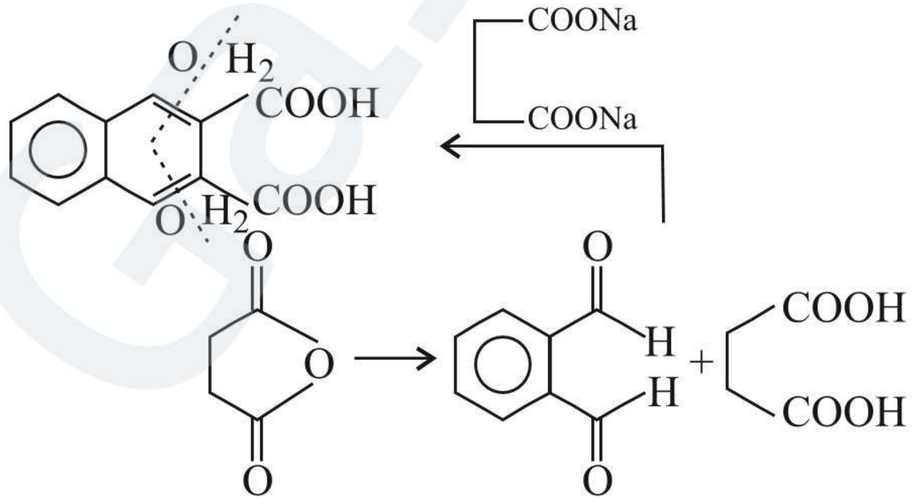


5.43.1 Intramolecular Perkin Reaction

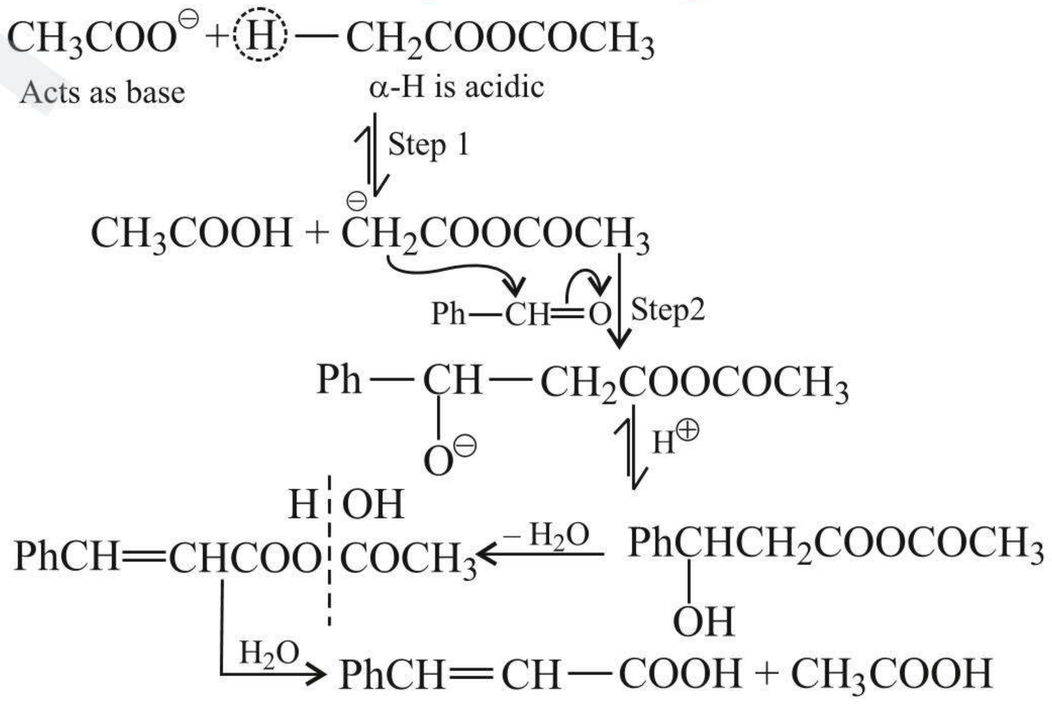
Aromatic aldehydes containing anhydride group (α-H atom) in the same molecule when heated with sodium salt of an aliphatic acid undergo intramolecular condensation to give cyclic α,β-unsaturated acid, e.g.,



5.43.2 Reverse Perkin Reaction



5.43.3 Mechanism (Aldol type)

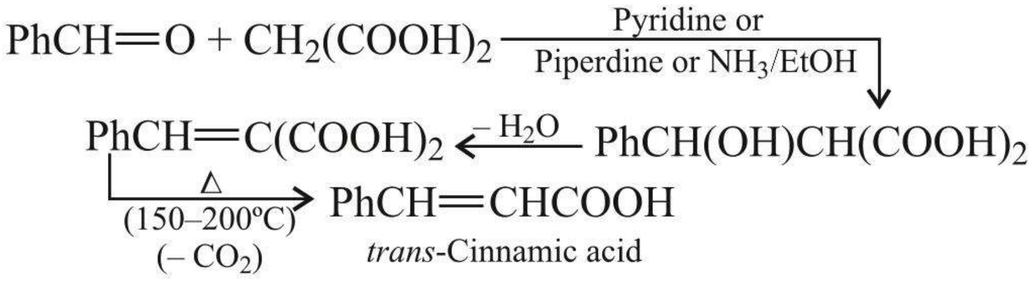


1. Perkin reaction does not usually take place with aliphatic aldehydes.

2. In some cases, (Et_3N) (triethyl amine) as base gives better yields.

5.44 KNOEVENAGEL REACTION

a. The condensation of aldehydes or ketones not containing an α-H atom with compounds containing an active methylene group of the type of Y-α-H atom -Y′ (Y and Y′ may be —CHO, —COR, —COOR, —COOH, —CN, —NO_2, etc.) in the presence of a weak base ($\ddot{O}R^{\ominus}$, $\ddot{O}H^{\ominus}$, $CH_3C\ddot{O}O^{\ominus}$, $R_3\ddot{N}$) is called Knoevenagel reaction, for example, a solution of malonic acid and benzaldehyde in pyridine on heating gives condensation product followed by dehydration to give α,β-unsaturated dibasic acid, which on heating is decarboxylated to yield α,β-unsaturated acid (cinnamic acid). It can take place with aldehyde having α-H atom.



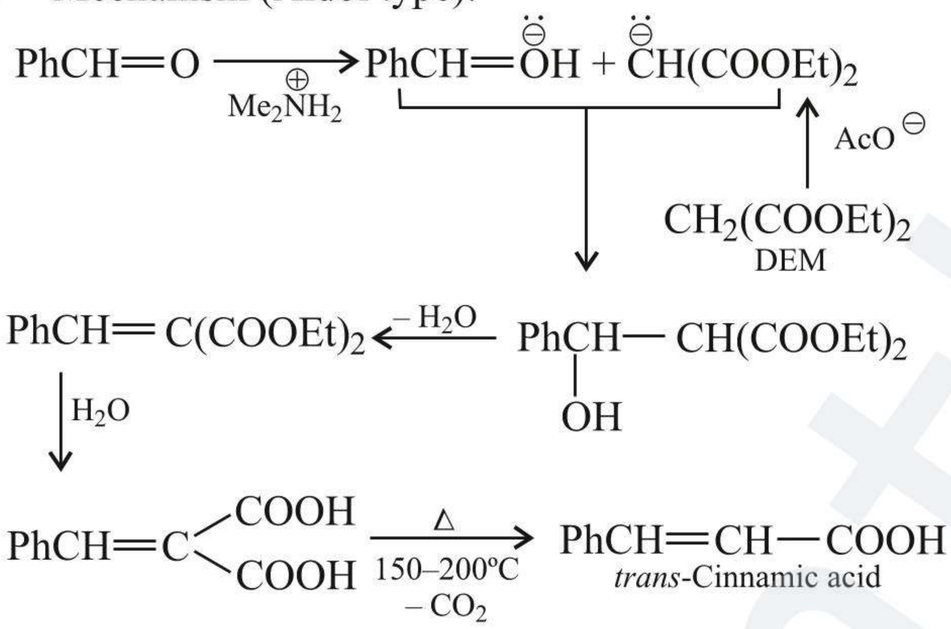
b. Base-catalysed condensation of (C═O) group with DEM or AAE containing active methylene group is not feasible:

The stable carbanion from DEM or AAE $\left(\overset{\ominus}{\underset{\cdot\cdot}{\cdot\cdot}}\!\!\text{CH(COOE)}_2 \text{ or } \overset{\ominus}{\underset{\cdot\cdot}{\cdot\cdot}}\!\!\text{CH}\begin{matrix}\text{COMe}\\ \text{COOEt}\end{matrix}\right)$ is not reactive enough to add to the (C═O) group.

A base is required to form the carbanion and an acid is required to activate the (C═O) group, which is achieved by a weak base ($RCOO^{\ominus}$) and a weak acid ($R_2\overset{\oplus}{N}H_2$). If a strong base and a strong acid is used, they would neutralise each other.

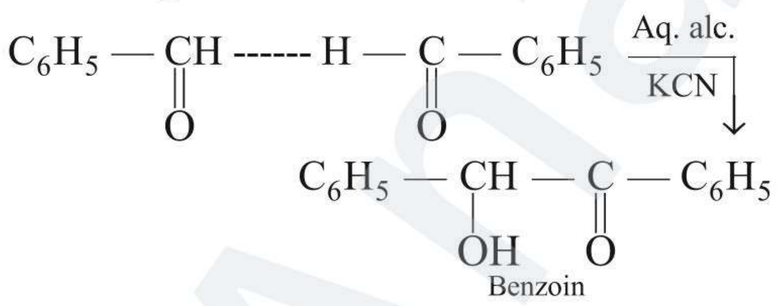
Due to this reason, the Knoevenagel reaction is successful with the weak acid ($R_2\overset{\oplus}{N}H_2$) which activates the aldehyde (PhCH═O) and the weak base ($RCOO^{\ominus}$) which activates the DEM or EAA.

c. Mechanism (Aldol type):

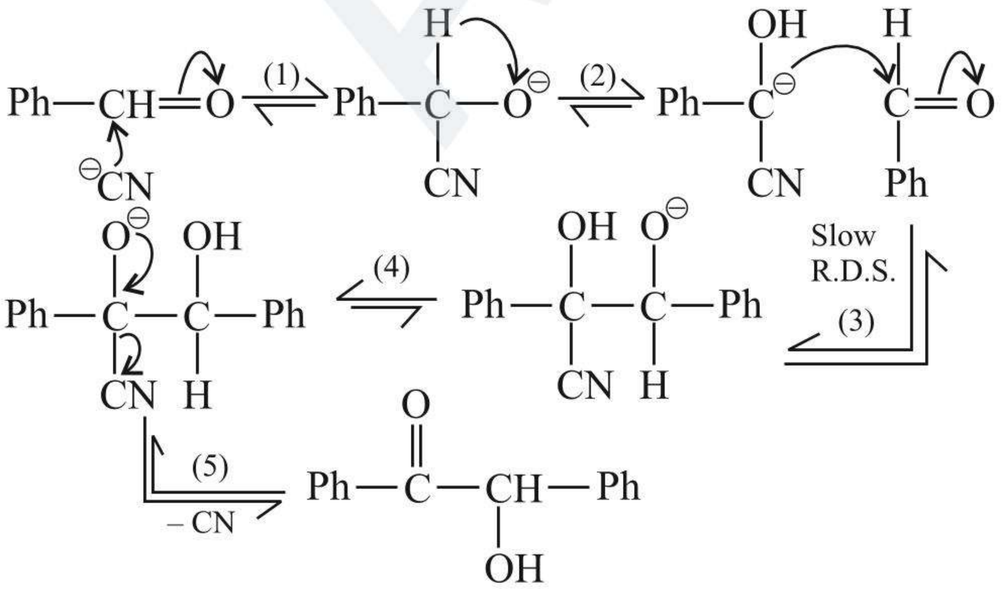


5.45 BENZOIN CONDENSATION

When benzaldehyde is refluxed with aq. alcoholic KCN solution to give benzoin (α-hydroxy ketone), the process is called benzoin condensation, e.g.,



5.45.1 MECHANISM



i. Cyanide is a very specific catalyst for benzoin condensation because it is a very weak base and a very good nucleophile. Further, its capacity to delocalise the negative charge on the carbon through mesomeric and inductive effect assists the formation of carbanion in step (2).

ii. Rate = $K[PhCHO]^2\,[CN^{\ominus}]$.

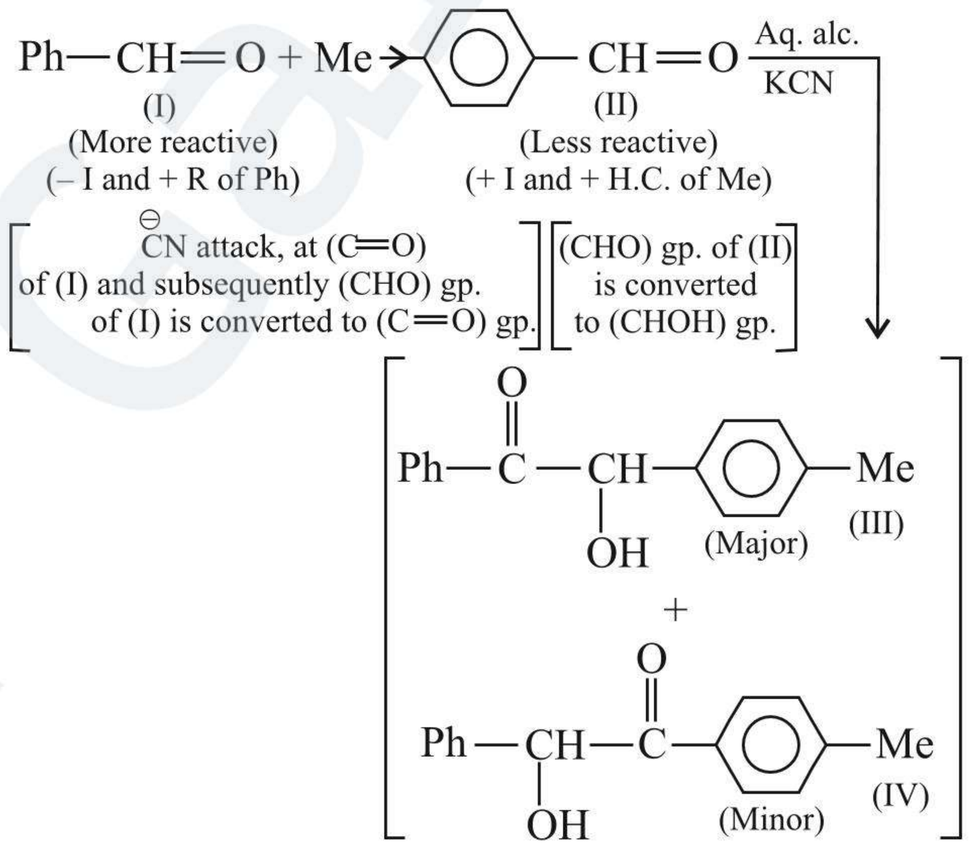
Step (3) is the rate-determining step.

iii. Such condensation can also be brought by Mg or amalgamated Al.

5.45.2 MIXED BENZOIN CONDENSATION

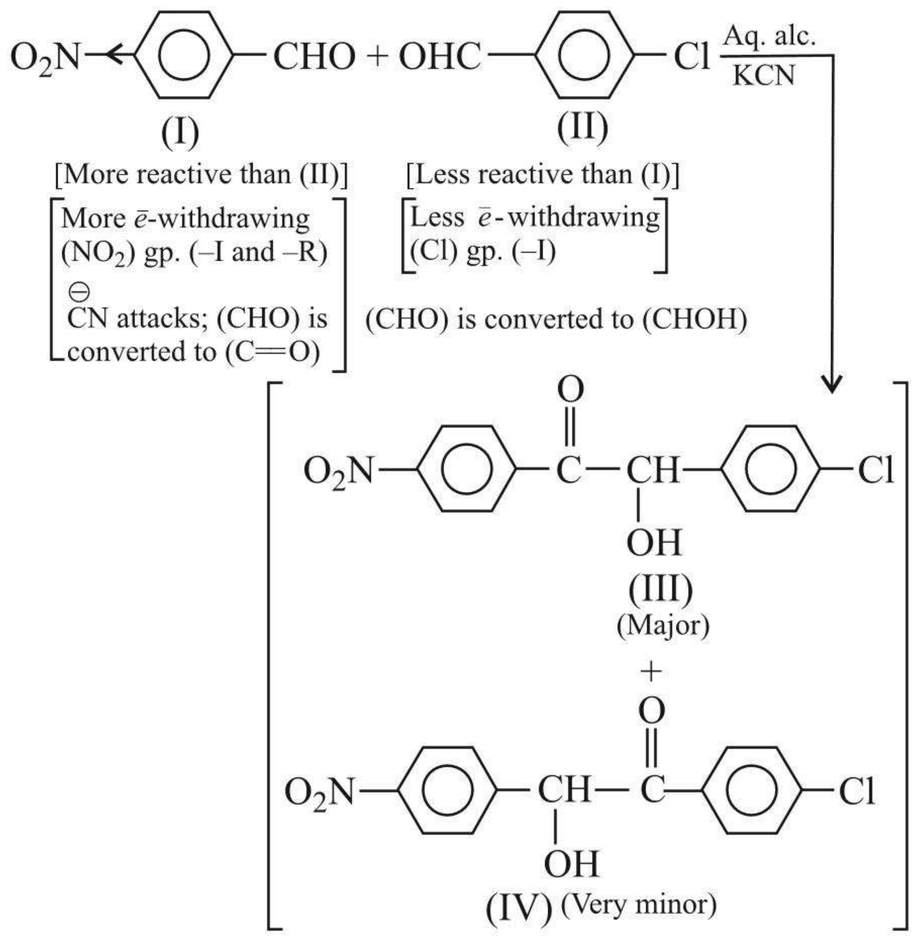
When two different aldehydes undergo benzoin condensation, the major product is formed from the more reactive aldehyde (containing $\bar{e}$ -withdrawing group at *o*- or *p*-position), e.g.,

i.

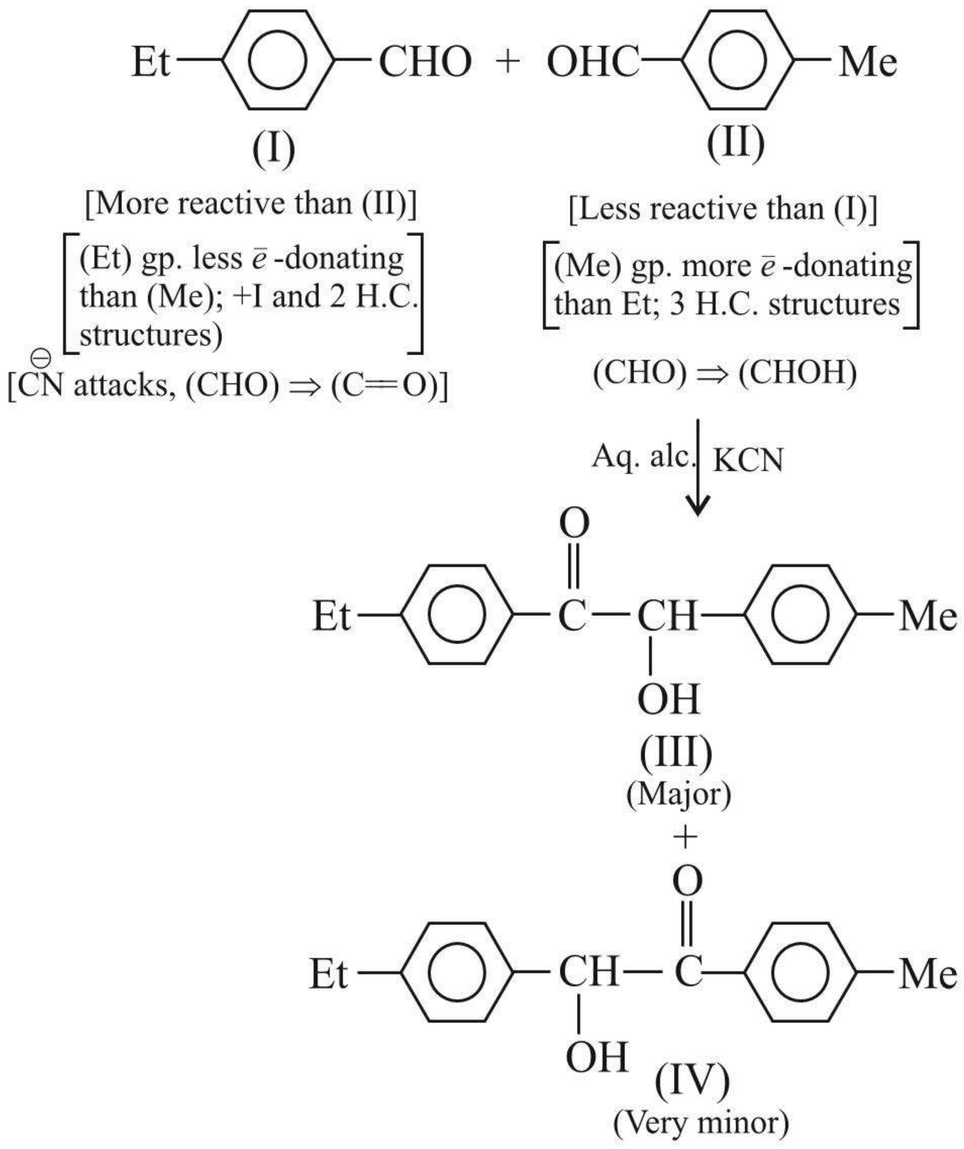


From the mechanism, it is clear that the nucleophilic addition (NA) reaction occurs with more reactive aldehyde (I), and it is the (CHO) group of the same aldehyde that is converted to (C═O) group. On the other hand, the (CHO) group of less reactive aldehyde is converted to (CHOH) group, giving product (III) in major amount.

ii.



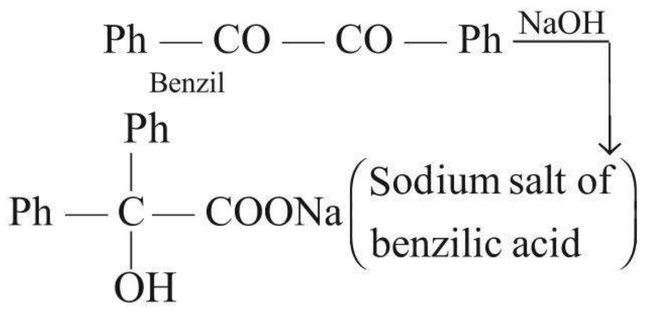
iii.



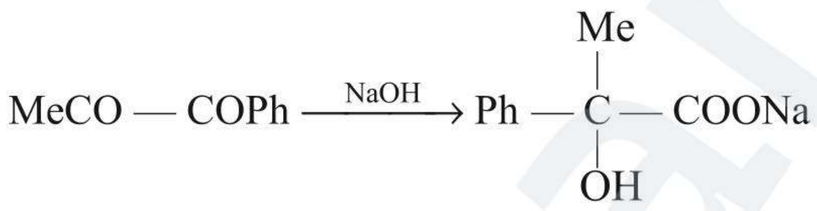
5.46 BENZIL–BENZILIC ACID REARRANGEMENT

α-Diketones undergo a rearrangement when treated with base (NaOH) to give α-hydroxy acids, e.g.,

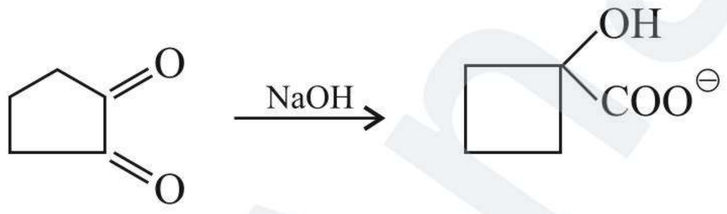
i.



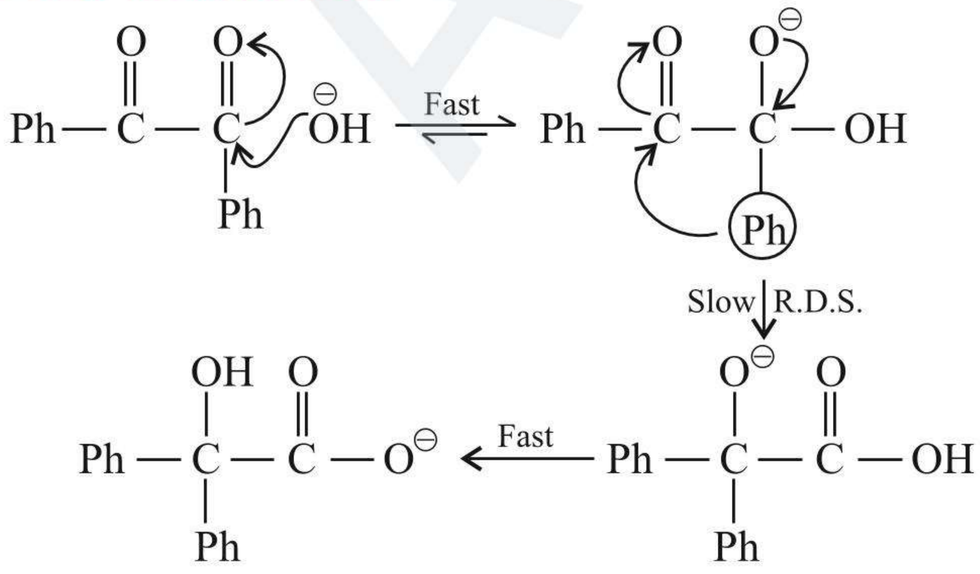
ii.



iii.



5.46.1 MECHANISM

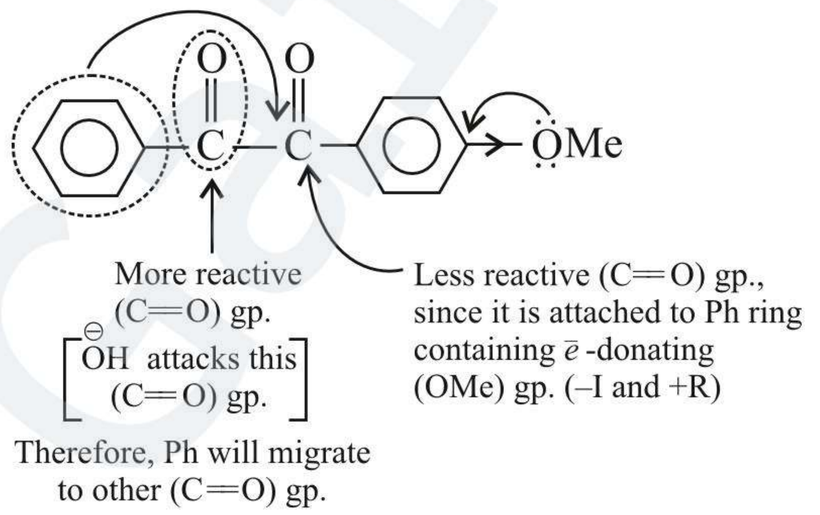


Rate = K[Benzil][$HO^{\ominus}$]

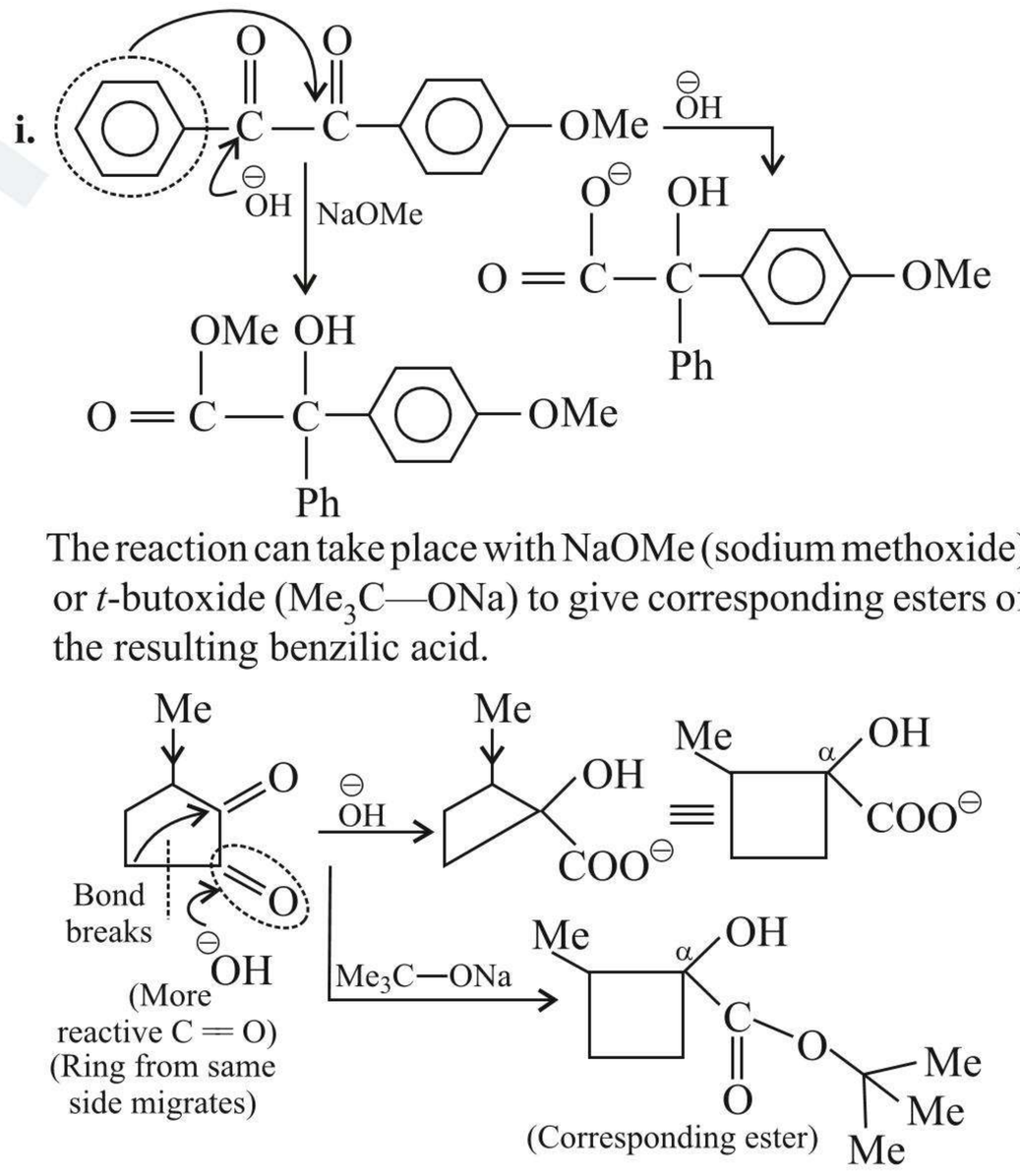
5.46.2 MIGRATING APTITUDE

When two aryl groups are different, the one with less $\bar{e}$ -donating substituent on the benzene ring will migrate. Thus, in the case of *p*-methyl benzil, the phenyl group migrates. The group that is more $\bar{e}$ -rich due to the presence of $\bar{e}$ -donating group on the benzene ring neutralises the positive charge on the C atom to which it is attached and consequently $\overset{\ominus}{O}H$ attacks the other carbonyl group.

Alternatively, out of the two (C═O) groups, nucleophilic addition (NA) reaction with $\overset{\ominus}{O}H$ will take place on the more reactive (C==O) group, which is attached to benzene ring containing $\bar{e}$ -withdrawing group. Thus, the same ring will migrate to other (C═O) group, giving α-hydroxy acid, e.g.,



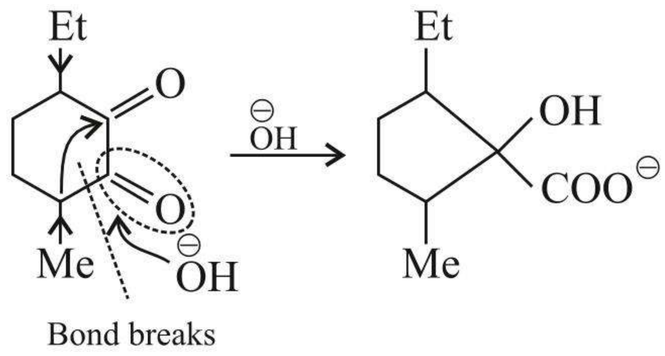
i.



The reaction can take place with NaOMe (sodium methoxide) or *t*-butoxide (Me_3C—ONa) to give corresponding esters of the resulting benzilic acid.

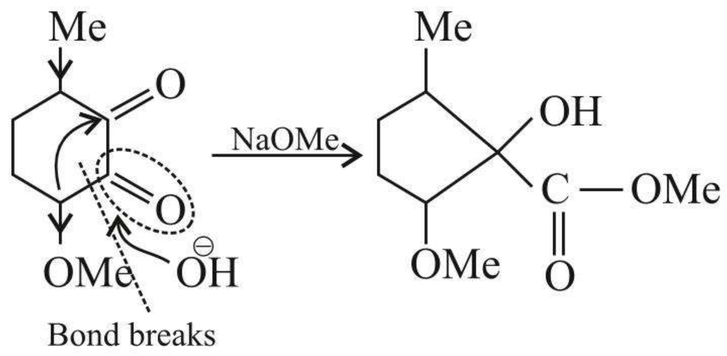
ii.

iii.



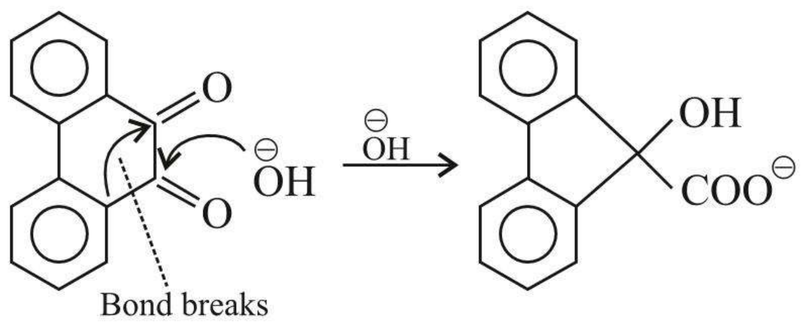
(+I effect of Et > Me). In this case, hyperconjugative effect (H.C.) does not operate because it is not attached to (C═C) or benzene ring.

iv.



The (OMe) group has only –I effect because it does not have any resonance. The reason being that it is not attached to the benzene ring. The (Me) group has only + I effect, and no H.C.

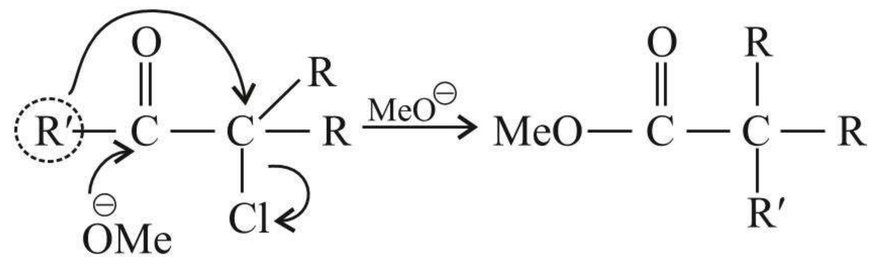
v.



Both (C═O) are equally reactive

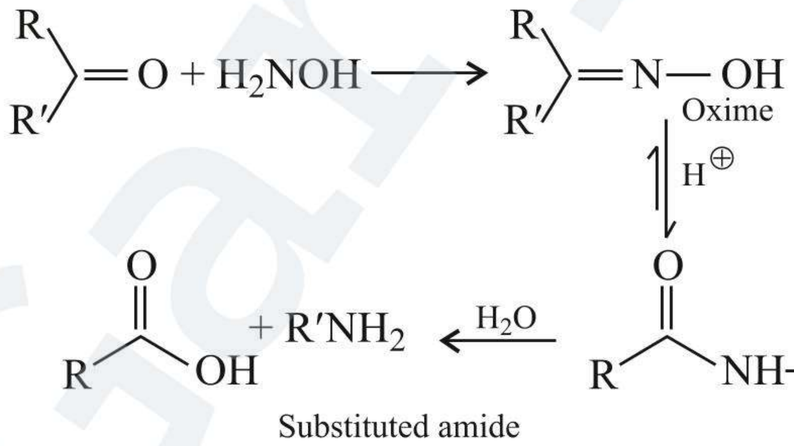
5.46.3 Semibenzilic Rearrangement

Similar benzilic acid rearrangement is observed when α-haloketones not having α-H atoms are treated with alkoxides. This is called Semibenzilic rearrangement.



5.47 Beckmann Rearrangement

Oximes of carbonyl compound undergo a rearrangement in the presence of mineral acids (H_2SO_4 or HCl or H_3PO_4) or Lewis acids (PCl_5, $PhSO_2Cl$, $SbCl_5$, $POCl_3$, $ArSO_3H$) to give substituted amides which on hydrolysis gives carboxylic acid and amines, e.g.,

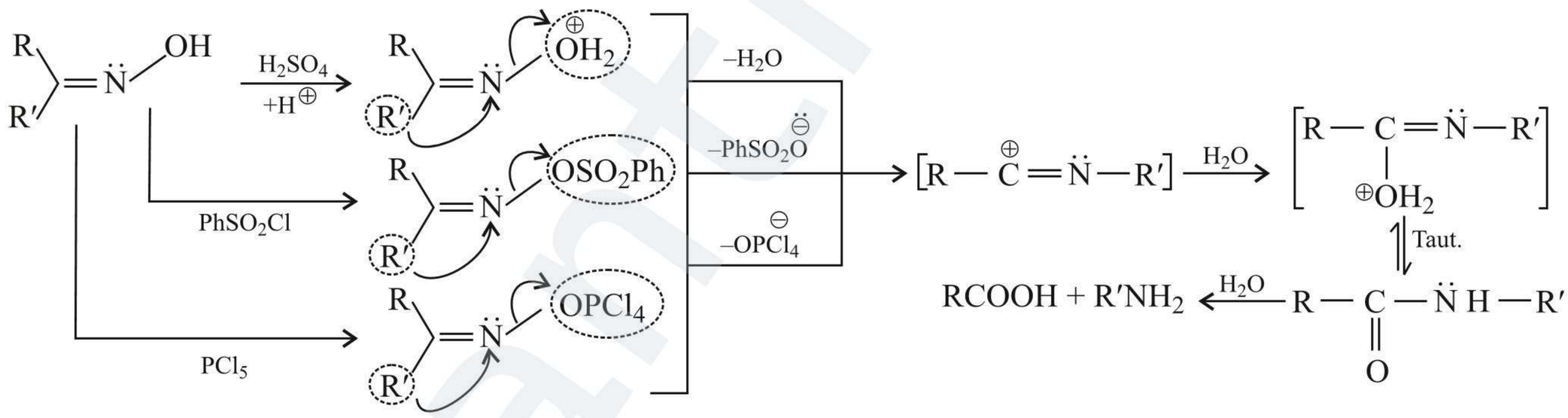


Substituted amide

5.47.1 Mechanism

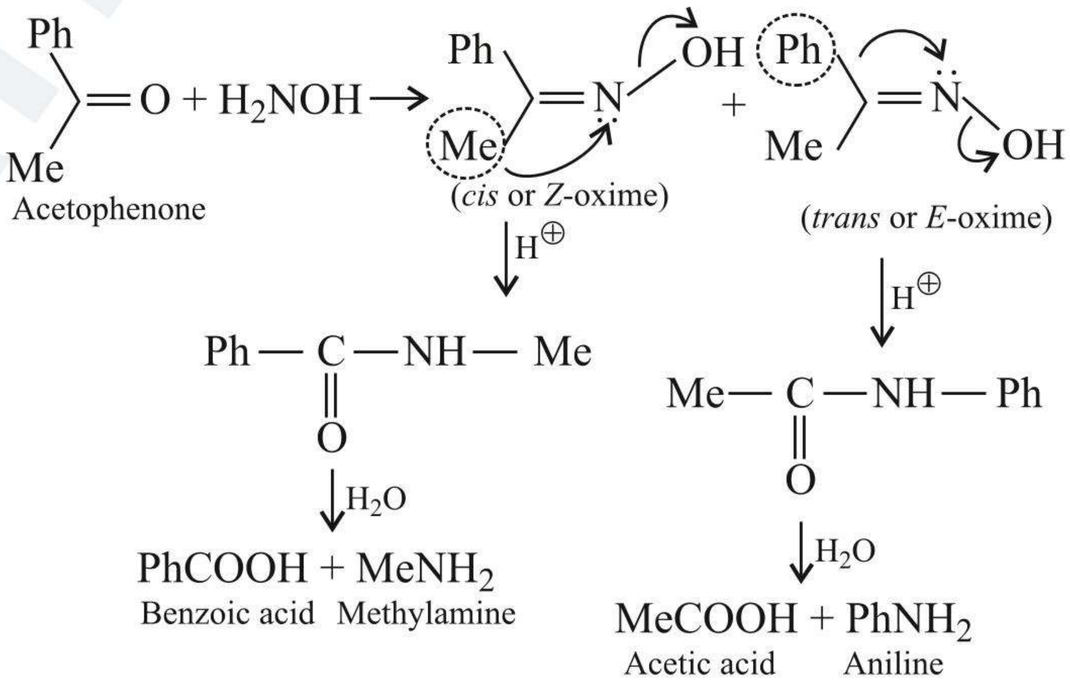
It is called anti-elimination, the group which is anti to the (OH) (leaving group) migrates from C to N atom.

The function of the acidic reagent is to convert the (OH) to a better leaving group.



Loss of H_2O or $PhSO_2O^{\ddot{\ominus}}$ or $OPCl_4^{\ominus}$ occurs with simultaneous migration of the anti (*trans*) R′.

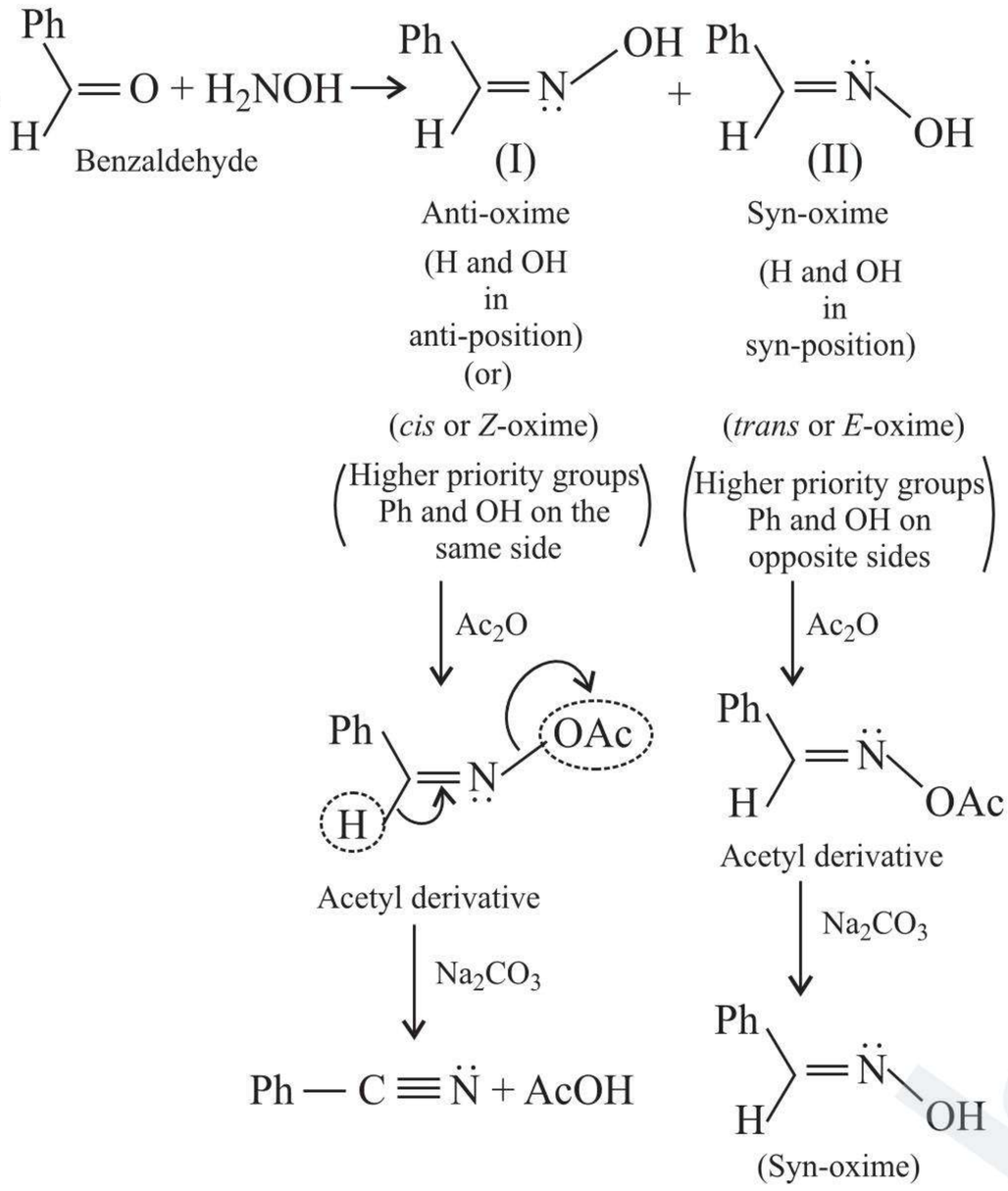
5.47.2 Anti-elimination



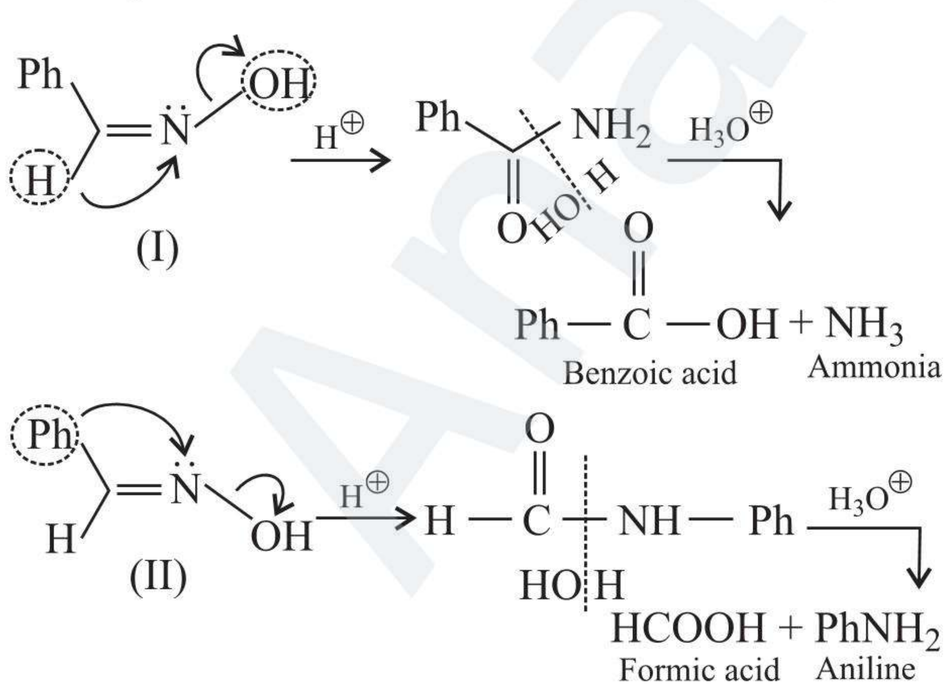
5.47.3 Determination of the Configuration of Aldoximes

The two isomeric aldoximes may be distinguished by the behaviour of their acetyl derivatives with aqueous Na_2CO_3.

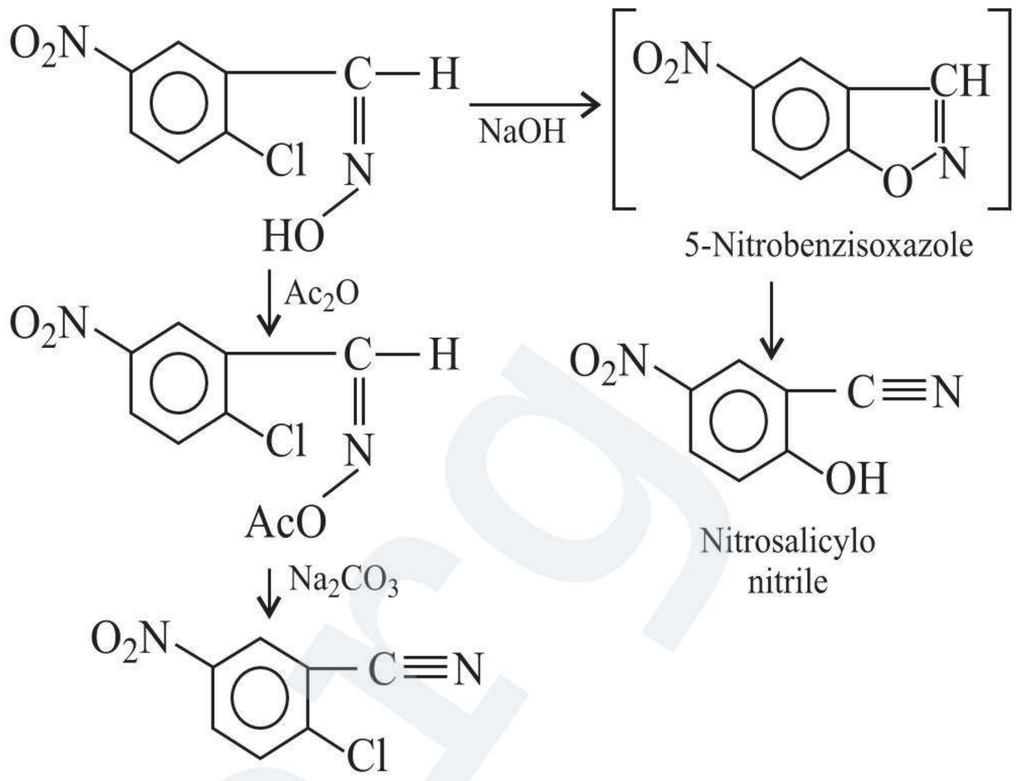
i.



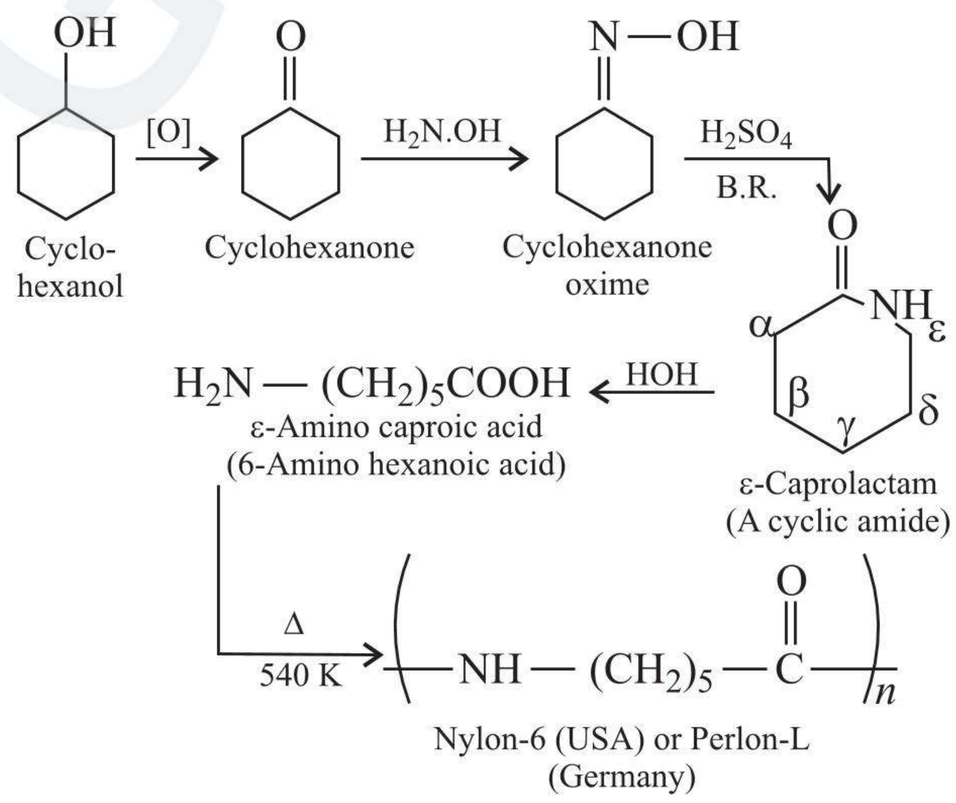
The acetyl derivative (syn or *E*) of aldoxime regenerates the oxime with aq. Na_2CO_3. This isomer is called α-isomer, whereas anti or *Z*-form of aldoxime with aq. Na_2CO_3 eliminates a molecule of acetic acid to form aryl cyanide, This form is called β-isomer. This shows that the cyanide is formed by anti-elimination. Therefore, anti-oxime (I) and syn-oxime (II) would give different products on Beckmann rearrangement.



ii. It was found that only one of the two isomers of 2-chloro-5-nitro-benzaldoxime readily gave ring closure on treatment with NaOH. This isomer is, therefore, the anti- (*trans*)-isomer. Moreover, it is this isomer whose acetyl derivative with Na_2CO_3 gives cyanide, thus showing that anti-elimination must have occurred.



5.47.4 Application of Beckmann Rearrangement Reaction: (Synthesis of Nylon-6 or Perlon-L)

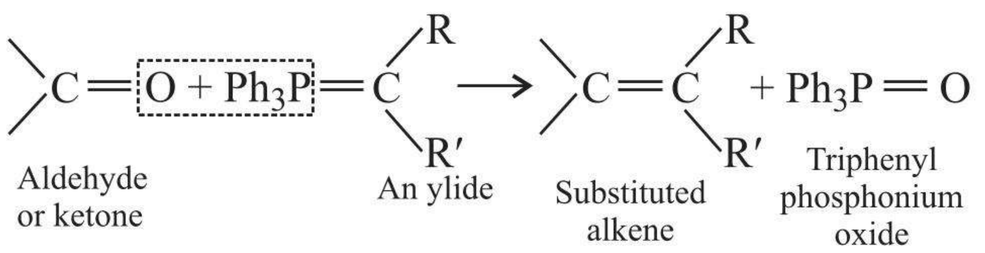


5.48 WITTIG REACTION

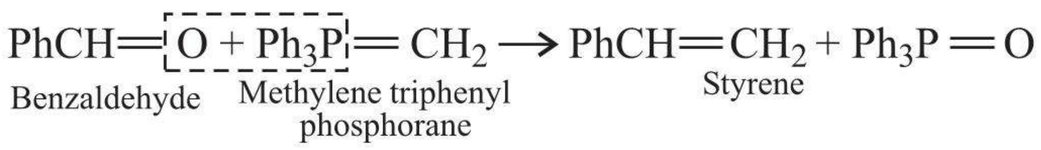
a. Aldehydes and ketones react with phosphorus ylides, e.g., alkylidene triphenyl phosphoranes ($Ph_3P{=}CRR'$) (where R and R′ may be alkyl or H atoms) to yield unsaturated compounds.

For example:

i.

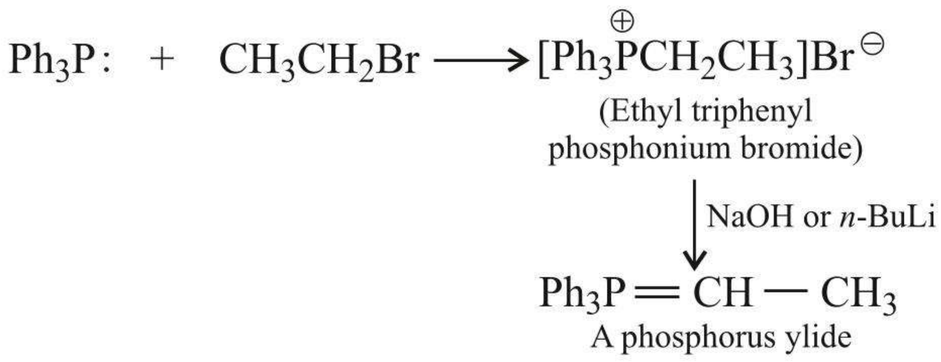


ii.



b. Mechanism:

The ylides are prepared by the reaction of triphenyl phosphorane $Ph_3\ddot{P}$ with RX, e.g.,

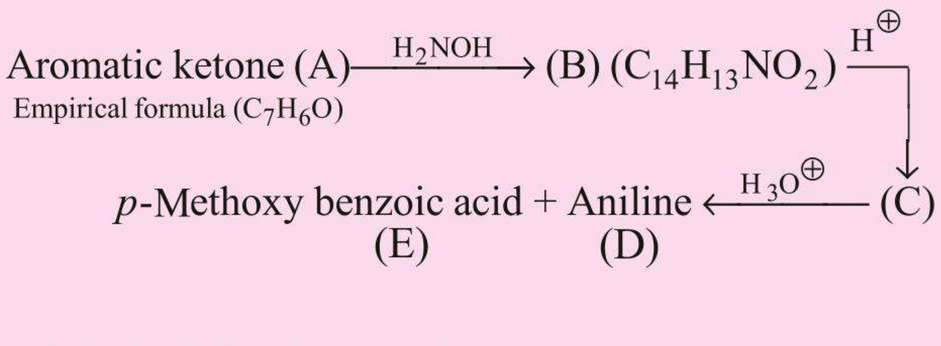


It is an example of SN^2 reaction. The nucleophile is $Ph_3\ddot{P}$ and the leaving group is $Br^{\ominus}$.

Order of reactivity of RX is $1° > 2° > 3°$.

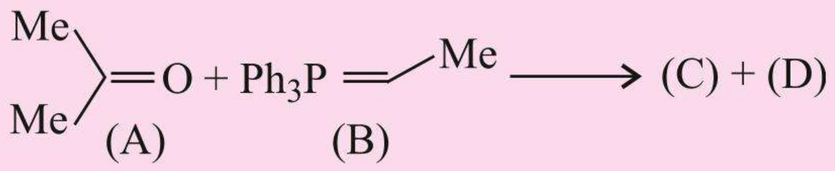
ILLUSTRATION 5.19

a. Identify (A) to (E) and name the stereoisomer of (B).

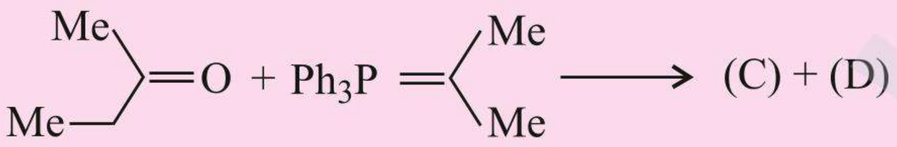


b. Complete the following reaction:

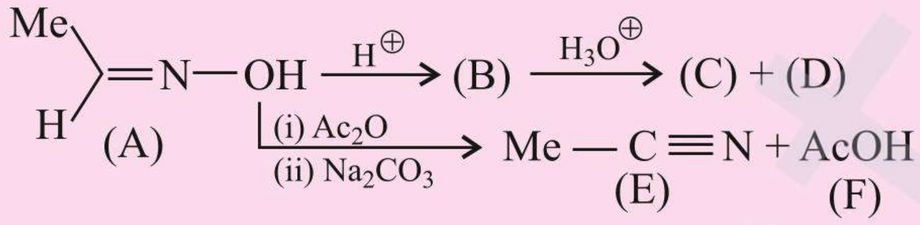
i.



ii.

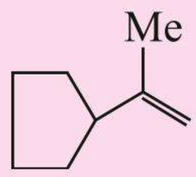


iii.



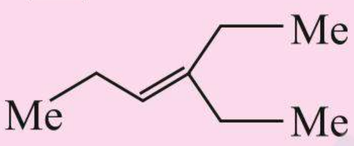
c. Give the structure of phosphonium halide, alkyl halide, and carbonyl compound used in the synthesis of following compounds by Wittig reaction.

i.



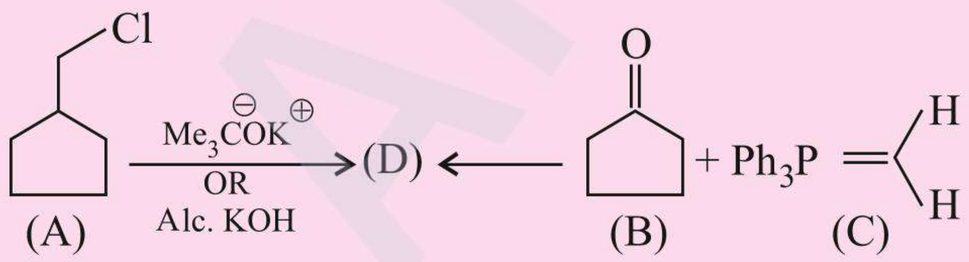
ii.

iii.

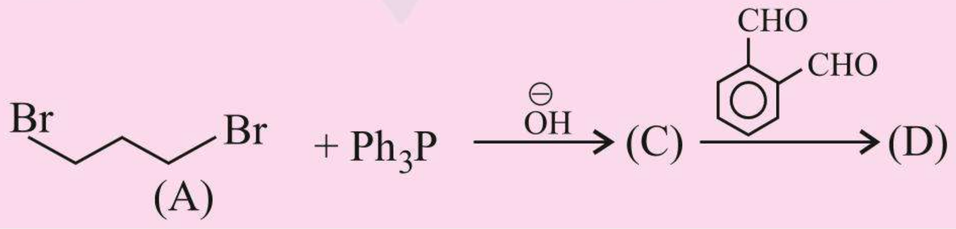


d. Complete the following reactions:

i.



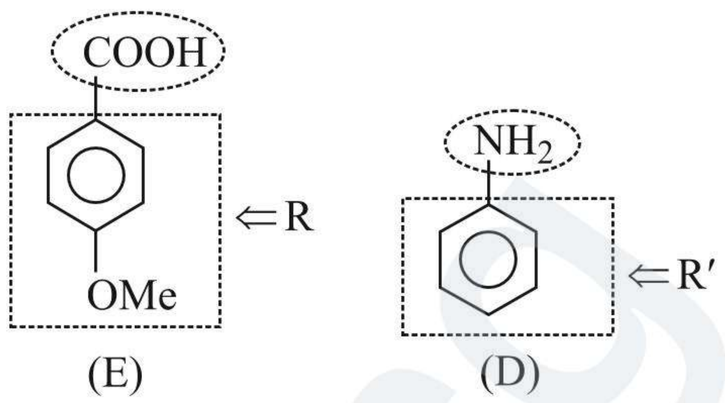
ii.

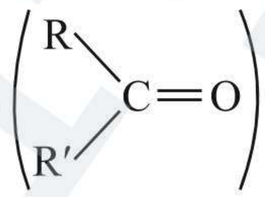


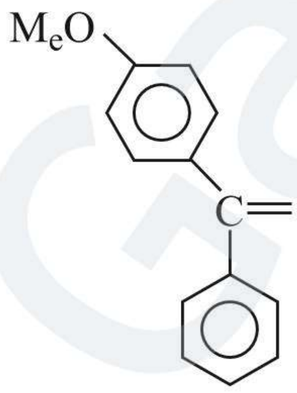
Sol. **a.**

i. Proceed reverse:

Write the structure of (E) and (D) followed by the removal of (—COOH) group from (E) and (—NH_2) from (D) to get the structure of R and R′ of ketone (A). Substitute R and R′ in (C═O) group, to obtain the structure of (A).



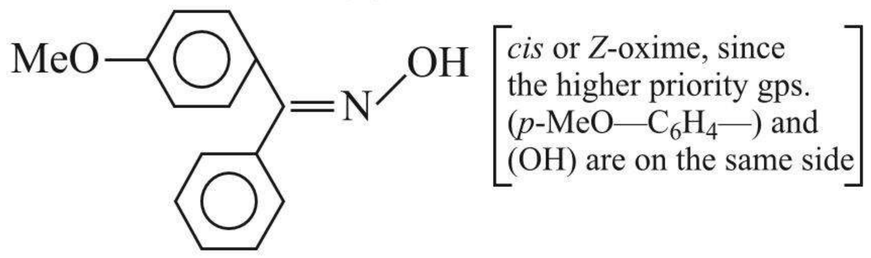
The structure of (A) is: 



ii. **Procedure for obtaining the stereoisomers of oxime:**

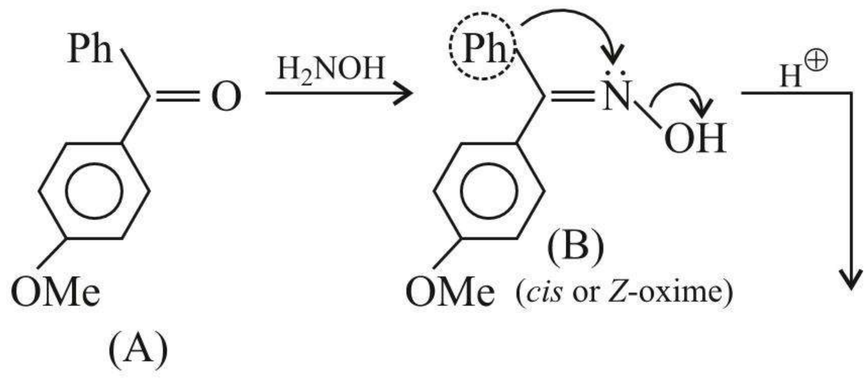
It is evident from the mechanism that the group which is anti to (OH) group has migrated from C to N, therefore R′ in amine has migrated. Substituting R′ and (OH) group in oxime in anti-position gives the stereoisomer of oxime.

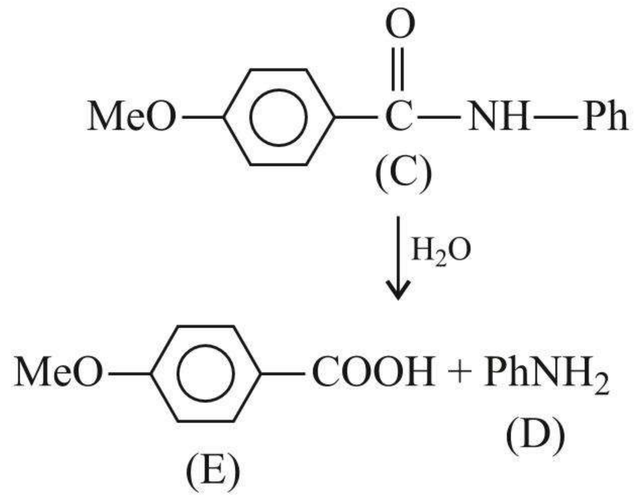
Structure of oxime (B):



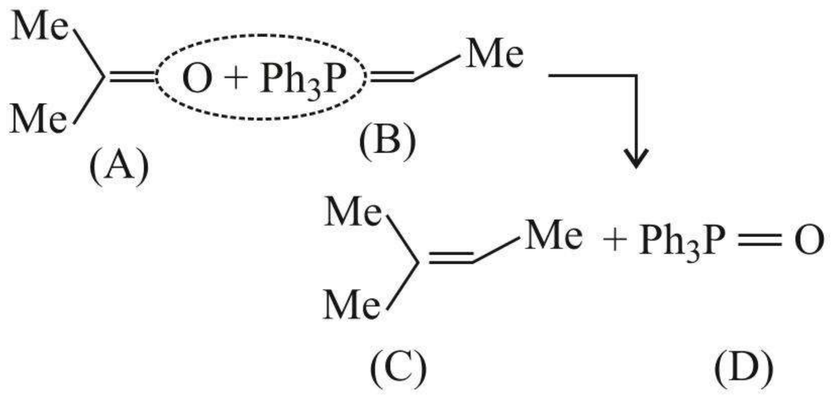
Alternatively, remember that the group which is attached to (—NH_2) group in amine has migrated. This group and (OH) would always be in anti-position in oxime.

Reactions:

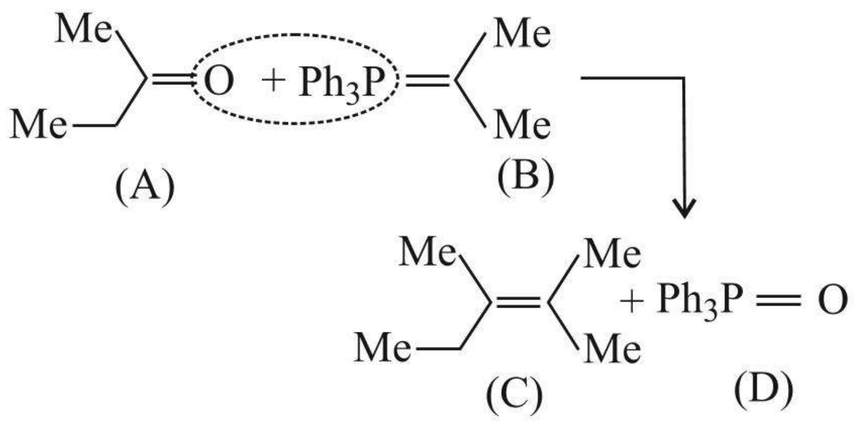




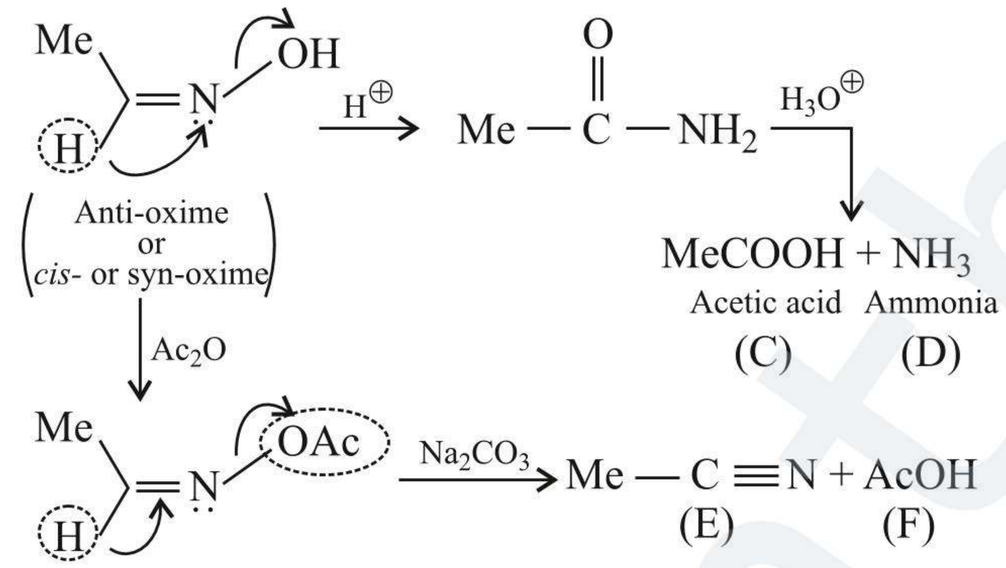
b. i.



ii.



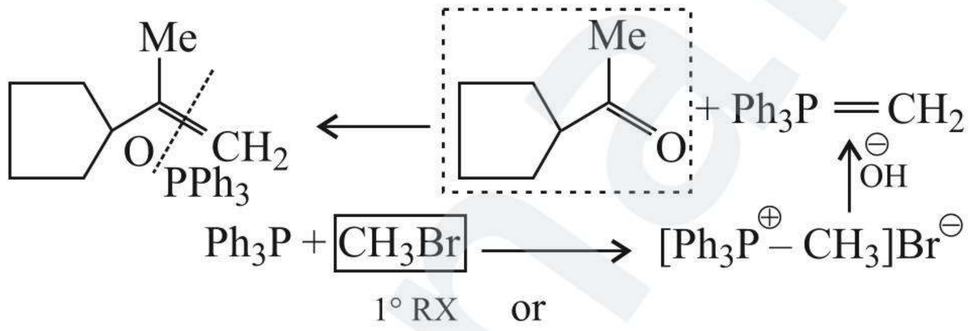
iii. Since the stereoisomer of oxime (A) is not given, the Beckmann reaction products (C) and (D) can not be determined. But the formation of cyanide (E) by the reaction of acetylated product of oxime (A) with Na_2CO_3 shows that oxime is anti (w.r.t. the position of H and OH).



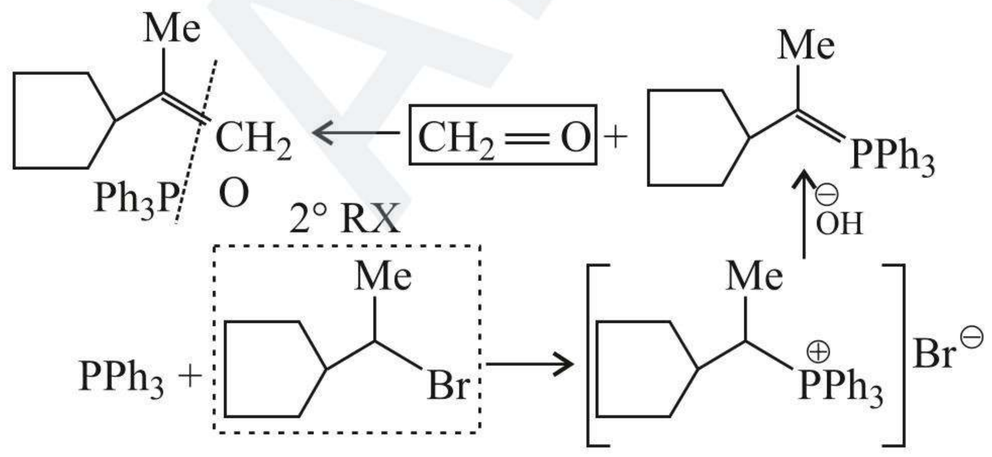
c. Proceed reverse:

(First method)

i.

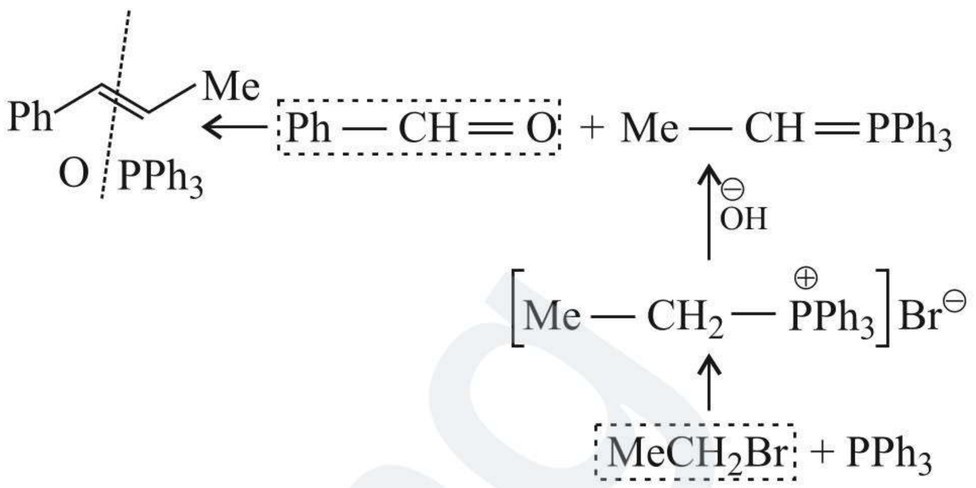


(Second method)

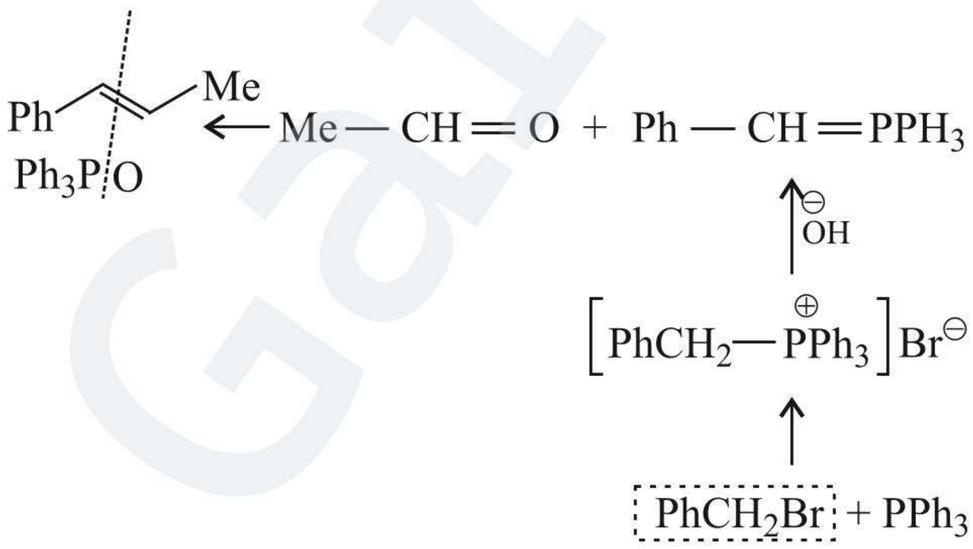


First method is better than the second method because RX used in it is 1° RX. Reactivity of SN^2 reaction is $1° > 2° > 3°$.

ii. Proceed reverse:

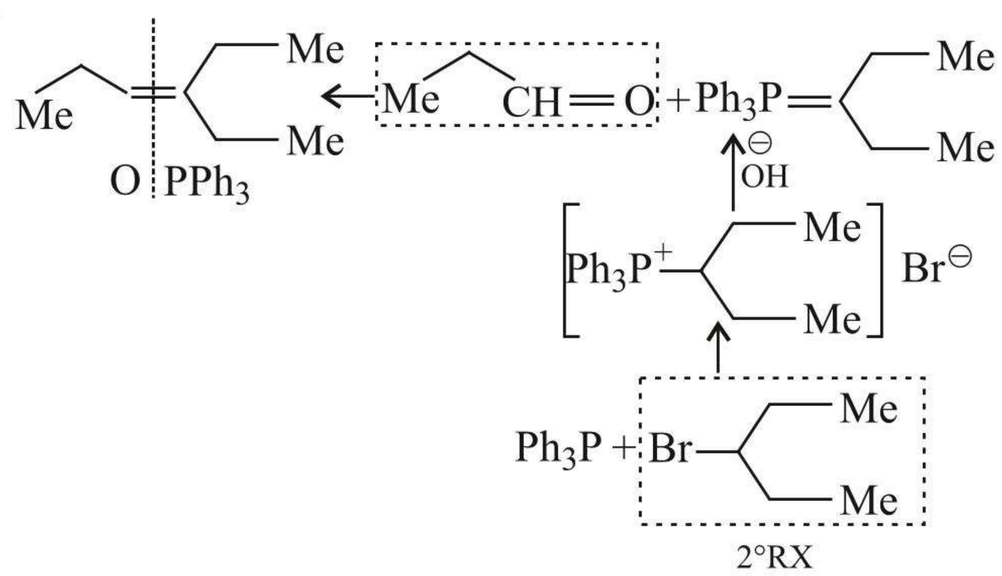


or



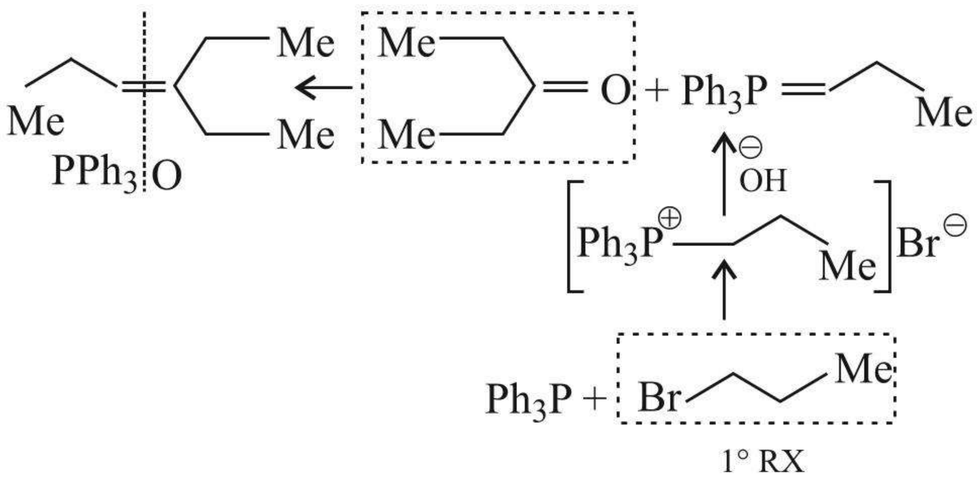
iii. Proceed reverse:

First method



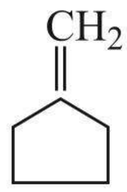
or

Second method

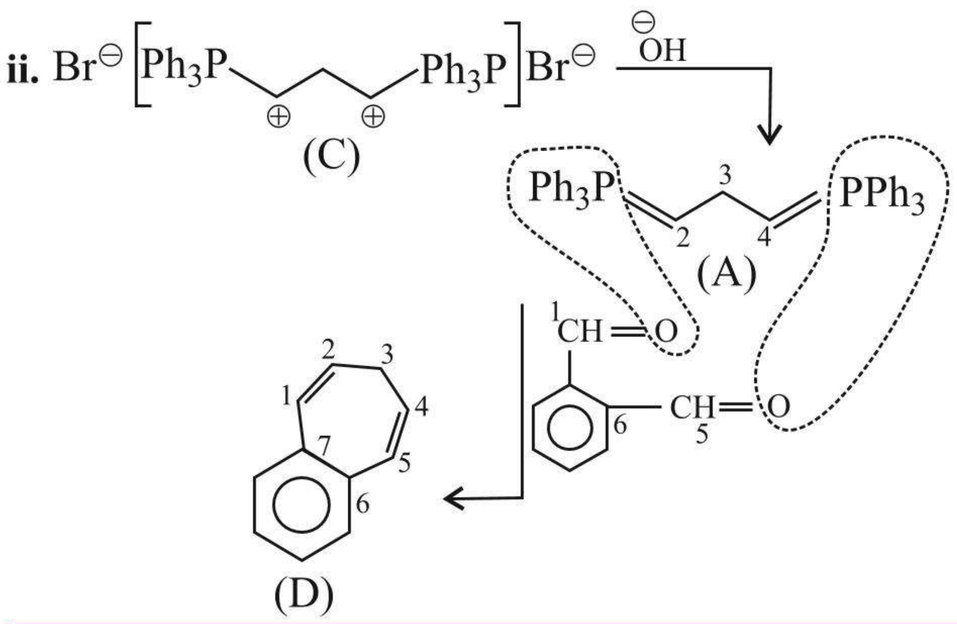


Second method is better than the first, since RX in this method is 1° RX.

d.i. (D) $\Rightarrow$

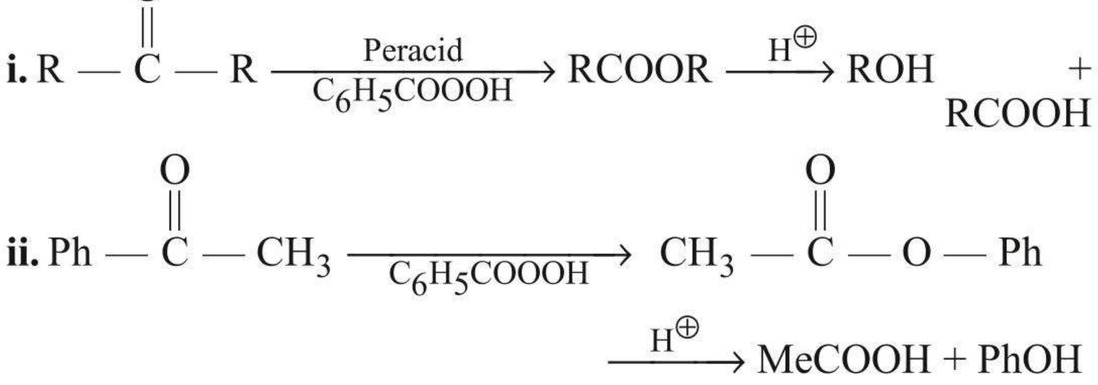


(Methylene cyclopentane)

ii. 

5.48.1 Baeyer–Villiger Oxidation

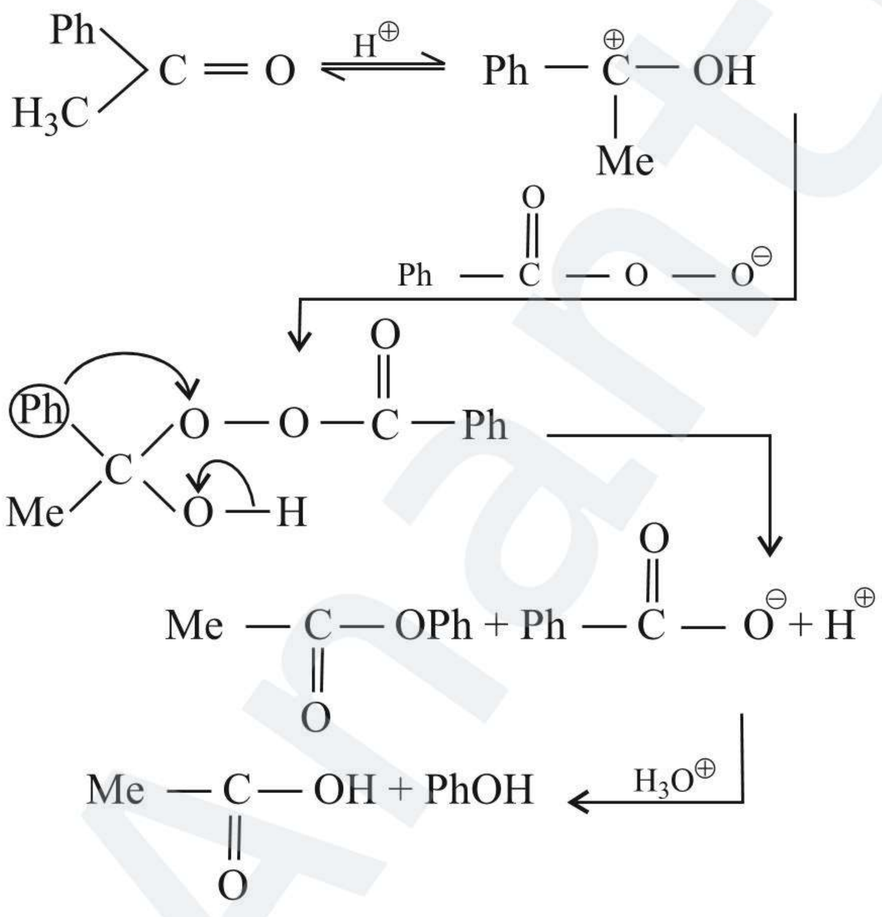
Ketone on treatment with peracid followed by hydrolysis gives acid and alcohol.

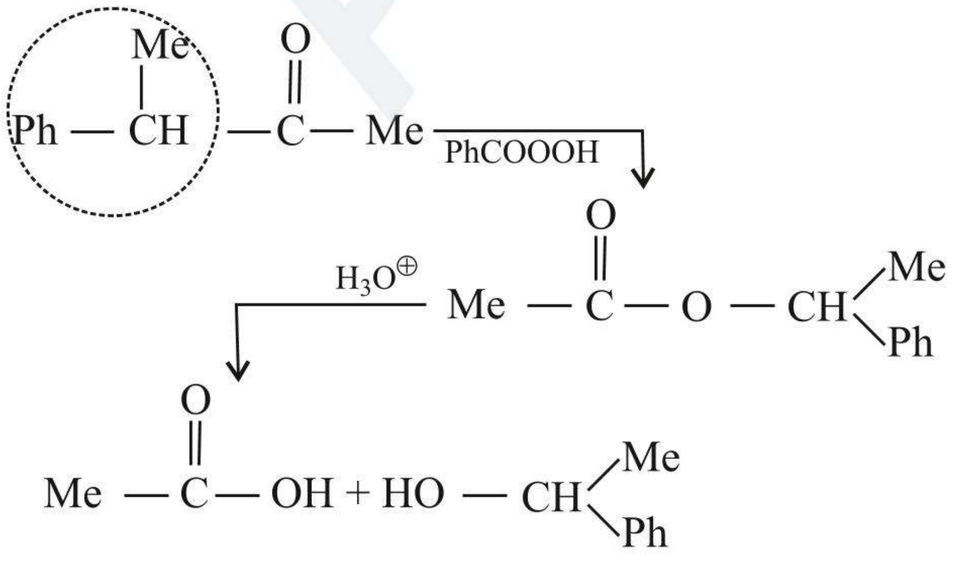


a. $\bar{e}$ -withdrawing group in peracid facilitates the reaction.

b. Strong $\bar{e}$ -donating group migrates. Aliphatic ketones are oxidised by H_2SO_5; aromatic ketone by peracetic or perbenzoic acid.

Mechanism:

i. 

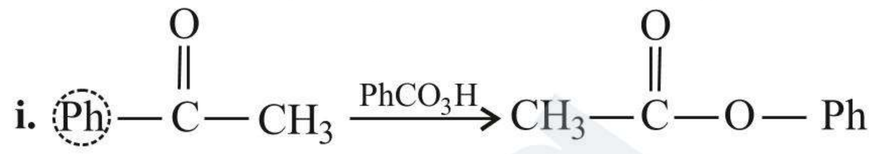
ii. 

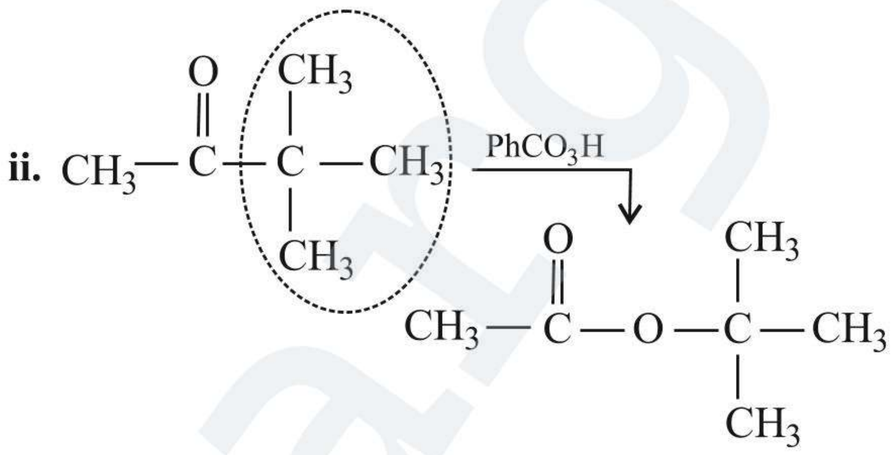
Migrating groups:

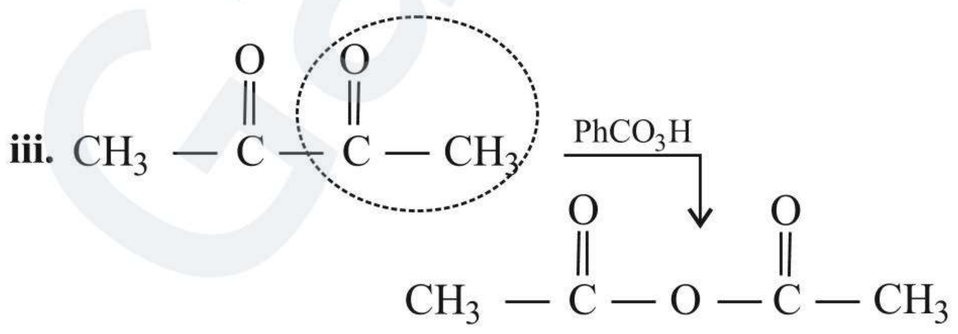
i. $3° > 2° > 1° C_2H_5- > CH_3-$,

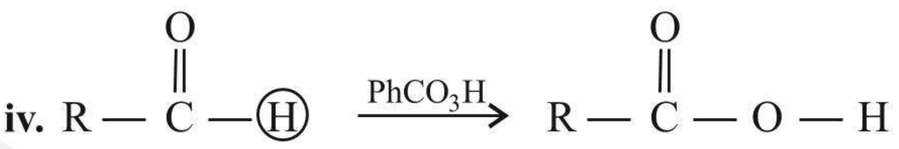
ii. *p*-anisyl > *p*-tolyl > Ph > *p*-ClPh > *p*-NO_2Ph,

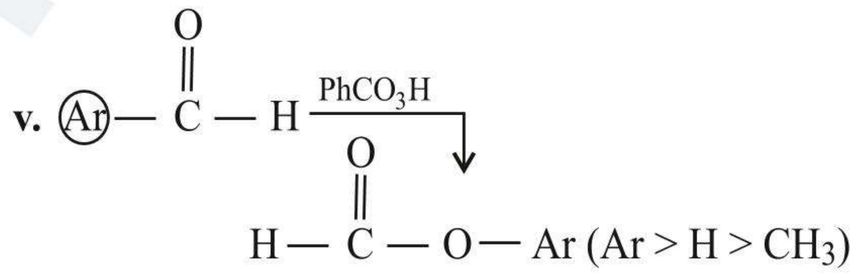
iii. Ar > H > CH_3. In case of alkyl aryl group, aryl group migrates (except in case of *t*-butyl group). For example,

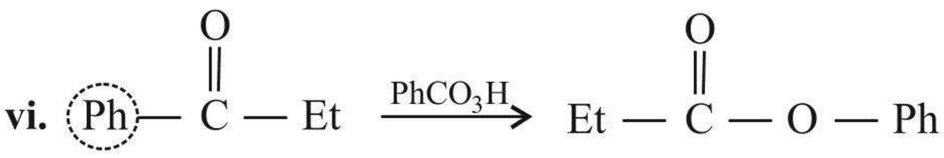
i. 

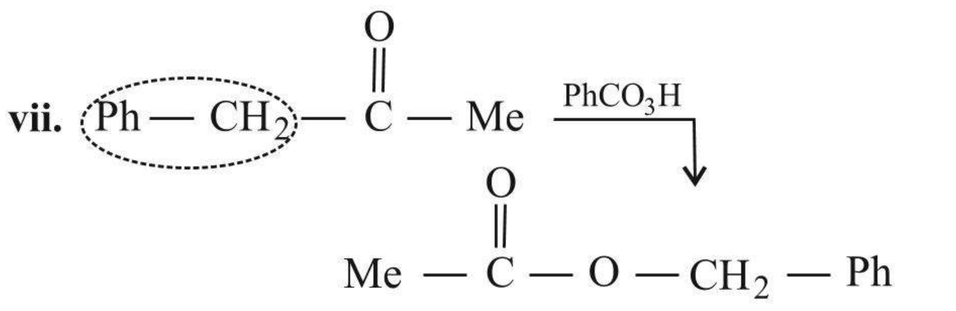
ii. 

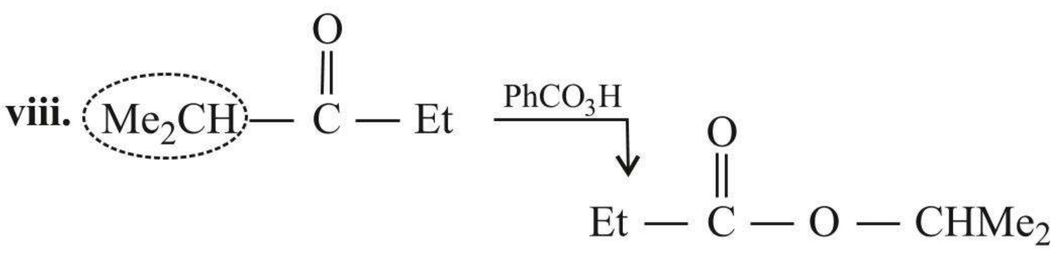
iii. 

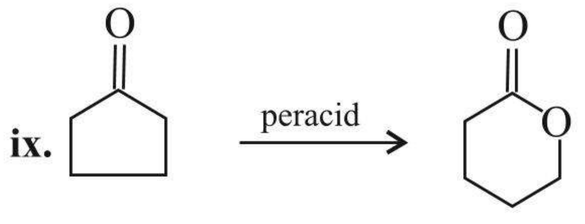
iv. 

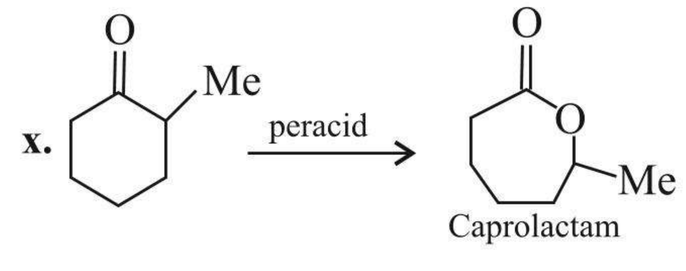
v. 

vi. 

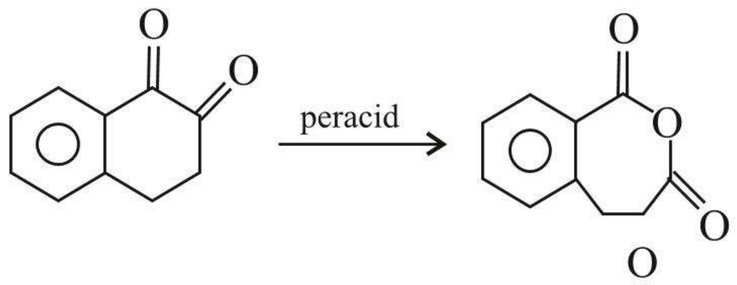
vii. 

viii. 

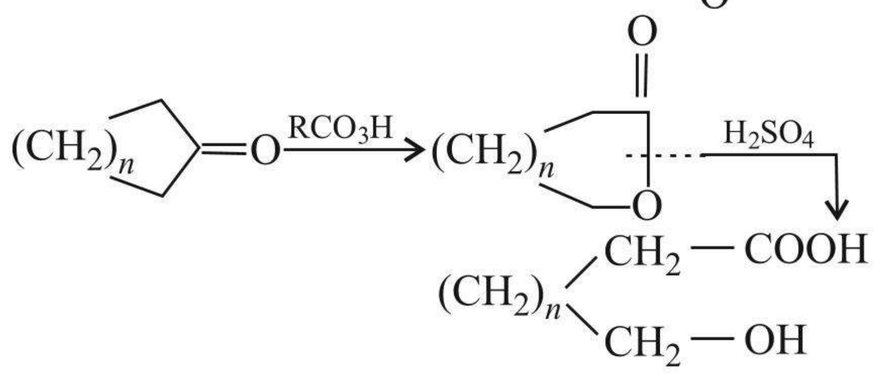
ix. 

x. 

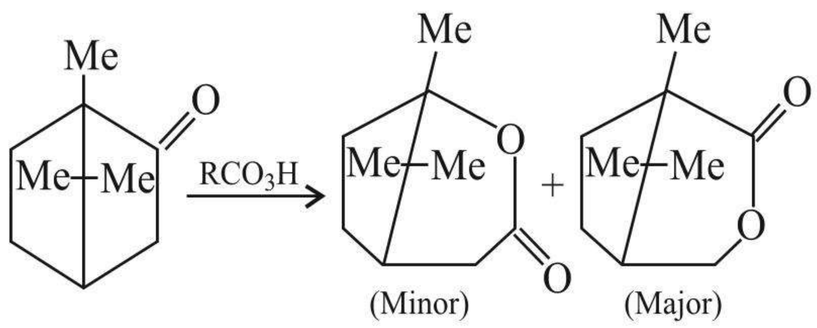
xi.



xii.

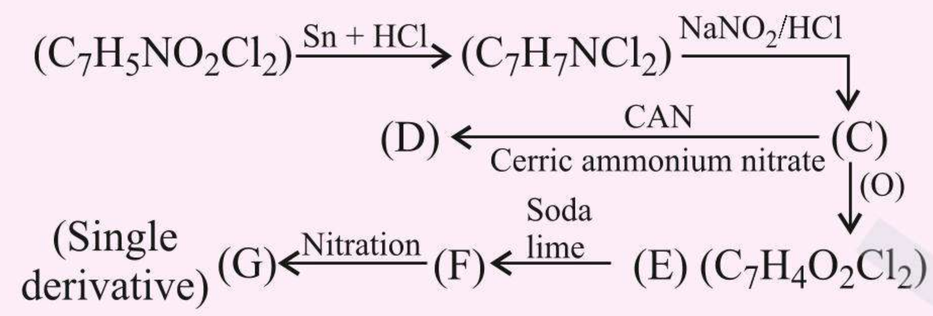


xiii.



Concept Application Exercise 5.3

1.



2. An aromatic ketone (X) has the molecular formula $C_{10}H_{12}O_2$. On vigorous oxidation, it yields a dibasic acid (Y) having the formula $C_9H_8O_5$ which rapidly forms an anhydride on heating. (X) on strong heating with sodium hypobromite gives monobasic acid (Z) with the formula $C_9H_{10}O_3$. (Z), when heated with soda lime, gives 3-methylanisole. Interpret the above reactions and deduce the structures of (X), (Y), and (Z).

3. An organic compound (A) ($C_8H_{14}O$) forms an oxime and gives a positive haloform reaction. On ozonolysis, it gives acetone and a compound (B) ($C_5H_8O_2$). (B) forms a dioxime and on subjecting to oxidation reaction gives an acid (C) ($C_4H_6O_4$). On treatment with excess of ammonia and strong heating, (C) gives a neutral compound (D) ($C_4H_5O_2N$). (D) on distillation with zinc dust forms pyrrole. Suggest the possible structures of (A), (B), (C), and (D). Explain the chemical reactions involved.

4. Hydrocarbon (X), C_7H_{12}, on reaction with boron hydride followed by treatment with CH_3COOH yields (A). On reductive ozonolysis (A) yields a mixture of two aldehydes, (B) and (C). Of these, only (B) can undergo Cannizzaro reaction. (A) exists in two geometrical isomers, (A – 1) and (A – 2), of which (A – 2) is more stable. Give structures of (X), (A), (B), (C), (A – 1), and (A – 2) with proper reasoning.

5. An organic compound (A) containing C, H, and O (16.32%) does not decolourise bromine water and does not give any precipitate with ammoniacal $AgNO_3$. It consumes 1 mol of NH_2OH per mole of (A) to give a solid derivative. The monobromo derivative of (A) shows optical activity. If (A) is optically inactive, suggest the structure.

6. Two organic compounds (A) and (B) containing 62.01% C and 10.3% H react with HCN in different manners to produce (C) and (D), respectively. Subsequent hydrolysis of (C) and (D) gives optically active compounds (E) and (F). Both (E) and (F) on decarboxylation give the same compound (G). Identify the compounds (A) to (G).

7. An organic compound (A) (C_5H_7OCl) reacts rapidly with ethanol to give (B) ($C_7H_{12}O_2$). (A) also reacts with water to produce an acid which reacts with bromine to give (C) ($C_5H_8Br_2O_2$). (B) on boiling with H_2SO_4 forms an acid (D). When (D) is oxidised with $KMnO_4$, an acid (E) ($C_4H_6O_3$) is produced. On mild heating, (E) gives (F) (C_3H_6O) which cannot be oxidised by ammoniacal $AgNO_3$. Identify the compounds (A) to (F).

8. An organic compound (A) contains 87.27% C and 13.73% H. Its vapour density is 55. Ozonolysis of (A) gives three compounds (B), (C), and (D). (B) undergoes a positive iodoform reaction and reacts with phenylhdrazine. Compounds (C) and (D) are not positive to Iodoform test. (C) on controlled oxidation gives (E) ($C_4H_6O_4$), which reacts with two equivalents of NaOH for complete neutralisation. (E) on heating above its melting point yields (F) ($C_4H_4O_3$) along with H_2O. Compound D reacts with NaOH solution to form (G) and (H). Acidified solution of (G) yields with a volatile acid (I) which reduces ammoniacal $AgNO_3$ solution. (I) undergoes reduction with $LiAlH_4$ to produce (H). Assign structures for the lettered compounds (A) to (I).

9. An organic compound (A) C_4H_9Cl on reacting with aqueous KOH gives (B) and on reaction with alcoholic KOH gives (C), which is also formed on passing the vapours of (B) over the heated copper. The compound (C) readily decolourises bromine water. Ozonolysis of (C) gives two compounds (D) and (E). Compound (D) reacts with NH_2OH to give (F) and compound (E) reacts with NaOH to give an alcohol (G) and sodium salt (H) of an acid. (D) can also be prepared from propyne on treatment with water in the presence of Hg^{2+} and H_2SO_4. Identify (A) to (H) with proper reasoning.

10. An alkyne with five carbon atoms per molecule when passed through dilute sulphuric acid containing mercuric sulphate gives a compound which forms an oxime but has no effect on Fehling's solution. The compound on oxidation gives dimethyl acetic acid. It reacts with sodamide to form a hydrocarbon. What is the structure of the alkyne?